

# 4-(2-Fluorophenyl)-6-(1*H*-indol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile: a chain of rings built from N—H···N, C—H···N and C—H··· $\pi$ (arene) hydrogen bonds

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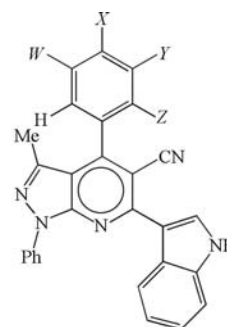
In the title compound, C<sub>28</sub>H<sub>18</sub>FN<sub>5</sub>, molecules are linked by a combination of N—H···N, C—H···N and C—H··· $\pi$ (arene) hydrogen bonds into complex double chains. The chains enclose cavities, four per unit cell, each of volume *ca* 102 Å<sup>3</sup> and apparently containing disordered solvent.

## Comment

We report here the structure of the title compound, (I), which we compare with the three analogues (II)–(IV) (see scheme) whose structures were reported fairly recently (Low *et al.*, 2007). As in the synthesis of compounds (II)–(IV), compound (I) was prepared by a multicomponent condensation reaction between 5-amino-3-methyl-1-phenylpyrazole, 3-(2-cyanoacetyl)indole and an aryl aldehyde, here 2-fluorobenzaldehyde, using microwave irradiation under solvent-free conditions. This method has been developed (Quiroga *et al.*, 2007) as a route for the introduction of an indolyl residue into substituted pyrazolo[3,4-*b*]pyridines in order to assess the influence of the naturally occurring indolyl group on the biological activity of the resulting synthetic products. The crystallization characteristics of compounds (I)–(IV) show some interesting variations which cannot be readily predicted or explained. Compounds (I) and (II) both crystallize in the space group *C2/c*, while (III) and (IV) both crystallize in *P1*. However, although compounds (II) and (III) crystallize as stoichiometric 1:1 solvates with dimethylformamide, and compound (IV) crystallizes in solvent-free form, compound (I) reported here contains an indeterminate quantity of solvent which could not be satisfactorily modelled from the diffraction data.

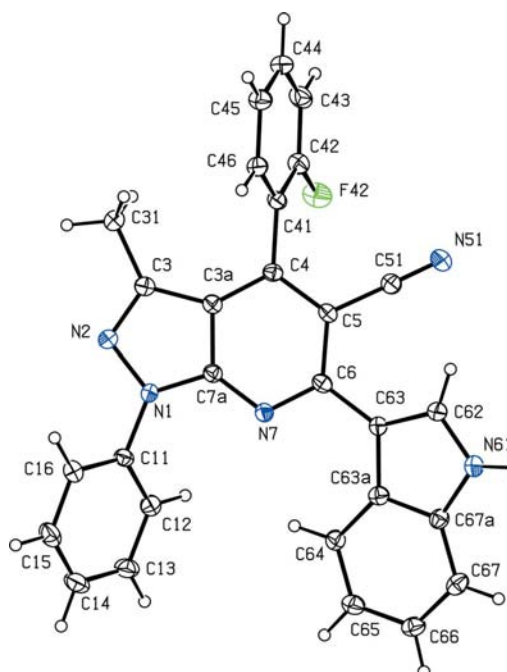
The pyrazolopyridine component of the molecule of (I) (Fig. 1) is effectively planar, with a maximum deviation from

the mean plane that of 0.067 (2) Å for atom C5; this slight deviation may be associated with the presence of three adjacent substituents, two of them bulky, at atoms C4–C6. It is interesting to note that the displacement of atom C51 from the mean plane of the bicyclic ring system [0.270 (2) Å] is in the opposite direction to the displacements of C41 and C63 [−0.053 (2) Å and −0.174 (2) Å, respectively], indicating that nonbonded repulsions between these substituents are probably the cause of the displacements. Due to this effective planarity, the molecular conformation can therefore be described in terms of just the three torsion angles (Table 1)



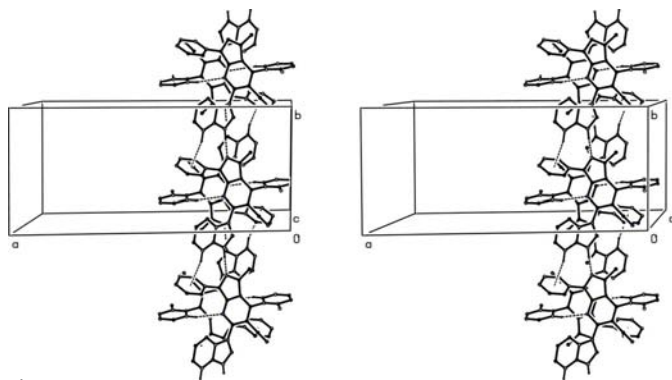
- (I)  $W = X = Y = \text{H}$ ;  $Z = \text{F}$   
 (II)  $W = Y = Z = \text{H}$ ;  $X = \text{Me}$   
 (III)  $W = Y = \text{H}$ ;  $X = \text{OMe}$ ;  $Z = \text{F}$   
 (IV)  $W = X = Y = \text{OMe}$ ;  $Z = \text{H}$

defining the orientation of the substituents relative to the pyrazolopyridine unit. The dihedral angles between the mean planes of the substituents and that of the pyrazolopyridine unit are 45.6 (2)° for the unsubstituted phenyl ring at N1,



**Figure 1**

The molecular structure of compound (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

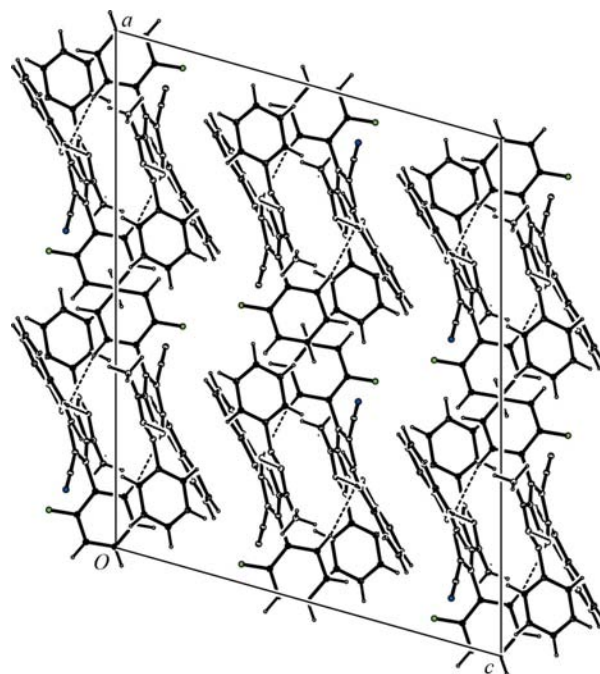
**Figure 2**

A stereoview of part of the crystal structure of compound (I), showing the formation of a complex hydrogen-bonded chain running parallel to the [010] direction. For the sake of clarity, H atoms not involved in the motifs shown have been omitted.

70.8 (2)° for the substituted phenyl ring at C4 and 25.1 (2)° for the indolyl unit at C6. Accordingly, the molecule of (I) has no internal symmetry and thus it is conformationally chiral, although the centrosymmetric space group accommodates equal numbers of the two conformational enantiomers. The bond distances and angles within the molecule of compound (I) show no unexpected values.

Three independent hydrogen bonds, one each of the N—H...N, C—H...N and C—H... $\pi$ (arene) types (Table 2), link the molecules of (I) into a complex chain of rings, or molecular ladder. The N—H...N hydrogen bond links molecules related by translation into a  $C(9)$  (Bernstein *et al.*, 1995) chain running parallel to the [010] direction; this chain formation is augmented by the C—H... $\pi$ (arene) hydrogen bond, so forming a chain of rings along [010]. Pairs of anti-parallel chains, related to one another by inversion, are then linked by paired C—H...N hydrogen bonds to form a complex chain of edge-fused rings in which  $R_2^2(14)$  rings centred at  $(\frac{1}{4}, n + \frac{1}{4}, \frac{1}{2})$ , where  $n$  represents an integer, alternate with  $R_4^4(26)$  rings centred at  $(\frac{1}{4}, n - \frac{1}{4}, \frac{1}{2})$ , where  $n$  again represents an integer (Fig. 2). The formation of the chain is weakly augmented by a  $\pi$ – $\pi$  stacking interaction involving pairs of pyridine rings: the pyridyl rings of the molecules at  $(x, y, z)$  and  $(\frac{1}{2} - x, \frac{1}{2} - y, 1 - z)$ , which form the  $R_2^2(14)$  motif, are strictly parallel, with an interplanar spacing of 3.674 (2) Å, a ring–centroid separation is 3.840 (2) Å and a ring–centroid offset of 1.117 (2) Å.

Four chains of this type run through each unit cell along the lines  $(\frac{1}{4}, y, 0)$ ,  $(\frac{1}{4}, y, \frac{1}{2})$ ,  $(\frac{3}{4}, y, 0)$  and  $(\frac{3}{4}, y, \frac{1}{2})$  (Fig. 3); there are no direction-specific interactions between adjacent chains, but instead these chains enclose cavities, totalling *ca* 9% of the unit-cell volume. There are four symmetry-related cavities per unit cell, each of volume *ca* 102 Å<sup>3</sup>, located on twofold rotation axes and centred close to  $(0, 0.335, \frac{1}{4})$ ,  $(0, 0.665, \frac{3}{4})$ ,  $(\frac{1}{2}, 0.835, \frac{1}{4})$  and  $(\frac{1}{2}, 0.165, \frac{3}{4})$ . Each cavity is bounded by a number of aromatic C—H bonds, along with F atoms and the N atoms belonging to nitrile units (Fig. 3). While significant electron density is located within the cavities, calculated by the SQUEEZE option in PLATON (Spek, 2009) as seven electrons per cavity, it did not prove possible to reconcile the

**Figure 3**

Projection of the hydrogen-bonded chains on to (010), indicating the location of the cavities. Accordingly, the H atoms have all been included.

distribution of electron density with any plausible array of disordered solvent molecules.

The supramolecular aggregation in compound (I) differs markedly from that observed for compounds (II) and (III) (Low *et al.*, 2007), as in these structures the single N—H bond is engaged in a hydrogen bond to the dimethylformamide component. Thus, in compound (II), a single C—H... $\pi$ (arene) hydrogen bond links the pyrazolopyridine units into centrosymmetric dimers from which the dimethylformamide units are pendent, while in compound (III), a combination of C—H...N and C—H... $\pi$ (arene) hydrogen bonds links the pyrazolopyridine units into a chain containing two types of ring, again with pendent solvent molecules. By contrast, the molecules of compound (IV), where no solvent component is present, are linked into simple  $C(12)$  chains by an N—H...O hydrogen bond. Hence, the hydrogen-bonding behaviour is different in each of compounds (I)–(IV). On the other hand, all four compounds exhibit a  $\pi$ – $\pi$  stacking interaction involving the pyridyl rings in pairs of molecules related by inversion. In compound (II), as in (I), this interaction augments the formation of a hydrogen-bonded dimer unit, in (III) it augments the chain formation, and in compound (IV) this interaction links a pair of antiparallel  $C(12)$  chains.

## Experimental

An equimolar mixture of 2-fluorobenzaldehyde, 5-amino-3-methyl-1-phenylpyrazole and 3-(2-cyanoacetyl)indole was subjected to microwave irradiation in the absence of solvent using a focused microwave reaction (CEM Discover) with maximum power 300 W for 9 min at a controlled temperature of 473 K. The reaction mixture was allowed to cool to ambient temperature and was then extracted with hot ethanol/dimethylformamide (2:1 v/v). The combined extracts

were reduced to a small volume and the resulting solid product was collected by filtration and washed successively with ethanol and diethyl ether to provide colourless crystals of (I) suitable for single-crystal X-ray diffraction (yield 83%, m.p. 570–571 K). MS (EI, 70 eV) *m/z* (%): 443 (100, *M*<sup>+</sup>), 350 (44), 140 (11), 77 (43), 51 (30).

#### Crystal data

$C_{28}H_{18}FN_5$	$V = 4604.0 (10) \text{ \AA}^3$
$M_r = 443.47$	$Z = 8$
Monoclinic, $C2/c$	Mo $K\alpha$ radiation
$a = 24.155 (3) \text{ \AA}$	$\mu = 0.08 \text{ mm}^{-1}$
$b = 10.5830 (7) \text{ \AA}$	$T = 120 \text{ K}$
$c = 18.712 (3) \text{ \AA}$	$0.45 \times 0.26 \times 0.25 \text{ mm}$
$\beta = 105.743 (10)^\circ$	

#### Data collection

Bruker–Nonius KappaCCD diffractometer	51259 measured reflections
Absorption correction: multi-scan (SADABS; Sheldrick, 2003)	5280 independent reflections
$T_{\min} = 0.968$ , $T_{\max} = 0.979$	3346 reflections with $I > 2\sigma(I)$
	$R_{\text{int}} = 0.065$

#### Refinement

$R[F^2 > 2\sigma(F^2)] = 0.069$	308 parameters
$wR(F^2) = 0.211$	H-atom parameters constrained
$S = 1.10$	$\Delta\rho_{\max} = 0.38 \text{ e \AA}^{-3}$
5280 reflections	$\Delta\rho_{\min} = -0.29 \text{ e \AA}^{-3}$

All H atoms were located in difference electron-density maps, and then treated as riding atoms in geometrically idealized positions with distances C–H = 0.95 (aromatic and heteroaromatic) or 0.98 Å (methyl) and N–H = 0.88 Å, and with  $U_{\text{iso}}(\text{H}) = kU_{\text{eq}}(\text{carrier})$ , where  $k = 1.5$  for the methyl group, which was permitted to rotate but not to tilt, and 1.2 for all other H atoms. Refinement based on the presence only of the pyrazolopyridine molecule converged to  $R = 0.141$ , with several unacceptably large peaks in the difference electron-density map. At this point, examination of the refined structure using *PLATON* (Spek, 2009) indicated the presence of four symmetry-related voids per cell, each of volume *ca* 102 Å<sup>3</sup>, located at  $(0, 0.335, \frac{1}{4})$ ,  $(0, 0.665, \frac{3}{4})$ ,  $(\frac{1}{2}, 0.835, \frac{1}{4})$  and  $(\frac{1}{2}, 0.165, \frac{3}{4})$ . Within each void, there were four residual peaks in a ‘T’-shaped arrangement, with the shaft of the ‘T’ lying along a twofold rotation axis, and an angle of *ca* 92° between the shaft and the crosspieces of the ‘T’; no plausible solvent model, for example, based upon two partially occupied methanol sites, could be developed from these peaks, hence the SQUEEZE option in *PLATON* was applied, which indicated seven electrons per void, and which led to an acceptable *R* factor, with satisfactory values for the electron-density residuals.

Data collection: *COLLECT* (Hooft, 1999); cell refinement: *DIRAX/LSQ* (Duisenberg *et al.*, 2000); data reduction: *EVALCCD* (Duisenberg *et al.*, 2003); program(s) used to solve structure:

**Table 1**

Selected torsion angles (°).

N2–N1–C11–C12	136.9 (2)	C5–C6–C63–C63a	–162.9 (2)
C3a–C4–C41–C42	–112.1 (3)		

**Table 2**

Hydrogen-bond geometry (Å, °).

*Cg* represents the centroid of the C11–C16 ring.

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N61–H61 $\cdots$ N2 <sup>i</sup>	0.88	2.10	2.953 (3)	163
C46–H46 $\cdots$ N7 <sup>ii</sup>	0.95	2.55	3.469 (3)	164
C67–H67 $\cdots$ Cg <sup>i</sup>	0.95	2.77	3.652 (2)	155

Symmetry codes: (i)  $x, y + 1, z$ ; (ii)  $-x + \frac{1}{2}, -y + \frac{1}{2}, -z + 1$ .

*SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXL97* and *PLATON*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SU3034). Services for accessing these data are described at the back of the journal.

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