Supramolecular aggregation in three 4-aryl-6-(1H-indol-3-yl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitriles

John N. Low,[a] **Justo Cobo,**[b] **Ana Sánchez,**[c] **Jorge Trilleras**[c] **and Christopher Glidewell**[d]*

[a]Department of Chemistry, University of Aberdeen, Meston Walk, Old Aberdeen AB24 3UE, Scotland, [b]Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain, [c]Grupo de Investigación de Compuestos, Heterociclícos, Departamento de Química, Universidad de Valle, AA 25360, Colombia, and [d]School of Chemistry, University of St Andrews, Fife KY16 9ST, Scotland

Correspondence e-mail: cg@st-andrews.ac.uk

Both 6-(1H-indol-3-yl)-3-methyl-4-(4-methylphenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile and 6-(1H-indol-3-yl)-3-methyl-4-(4-methoxyphenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile crystallize from dimethylformamide solutions as stoichiometric 1:1 solvates, viz. $C_{29}H_{21}N_5 \cdot C_3H_7NO$, (I), and $C_{29}H_{21}N_5O \cdot C_3H_7NO$, (II), respectively; however, 6-(1H-indol-3-yl)-3-methyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile, $C_{31}H_{25}N_5O_3$, (III), crystallizes in the unsolvated form. The heterocyclic components of (I) are linked by C—H···π(arene) hydrogen bonds to form cyclic centrosymmetric dimers, from which the solvent molecules are pendent, linked by N—H···O hydrogen bonds. In (II), the heterocyclic components are linked by a combination of C—H···N and C—H···π(arene) hydrogen bonds into chains containing two types of centrosymmetric ring, and the pendent solvent molecules are linked to these chains by N—H···O hydrogen bonds. Molecules of (III) are linked into simple C(12) chains by an N—H···O hydrogen bond, and these chains are weakly linked into pairs by an aromatic π–π stacking interaction.

Comment

We report here the structures of three 6-(1H-indol-3-yl)-3-methyl-1-phenyl-4-aryl-1H-pyrazolo[3,4-b]pyridine-5-carbonitriles, two of which crystallize from dimethylformamide solutions as stoichiometric monosolvates, namely 6-(1H-indol-3-yl)-3-methyl-1-phenyl-4-(4-methylphenyl)-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile dimethylformamide solvate, (I), 6-(1H-indol-3-yl)-3-methyl-1-phenyl-4-(4-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile dimethylformamide solvate, (II), and the solvent-free 6-(1H-indol-3-yl)-3-methyl-

1-phenyl-4-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile, (III) (Figs. 1–3). The heterocyclic components within this group differ only in the substituents on the pendent aryl ring (atoms C41–C46).

(I) R=Me
(II) R=OMe

(III)
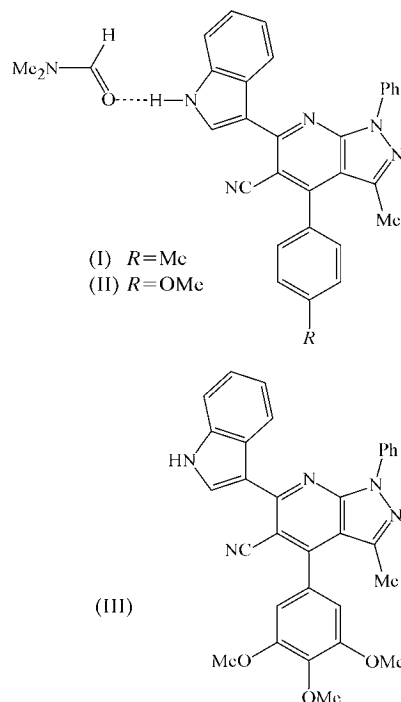
As a part of our exploration of routes to new biologically interesting pyrazolo[3,4-b]pyridine derivatives, we have sought methods for the introduction of an indolyl residue as a substituent at C-6 in order to establish the influence of this naturally occurring group on the biological activity of the resulting products. To this end, we have adapted the multi-
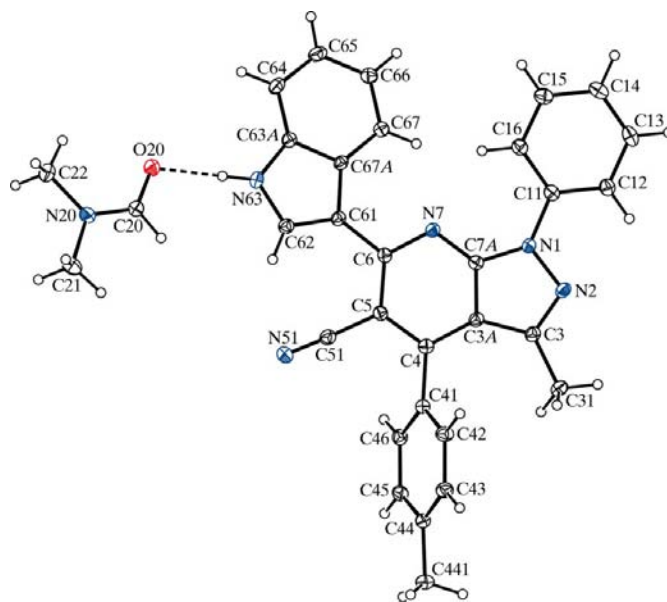

Figure 1
The independent components of (I), showing the atom-labelling scheme and the N—H···O hydrogen bond (dashed line) within the selected asymmetric unit. Displacement ellipsoids are drawn at the 30% probability level.

organic compounds

component reaction between substituted aryl aldehydes, an aminopyrazole and a ketone derivative, which has been used for the synthesis of fused heterocyclic systems (Quiroga *et al.*, 2007), to include the use of 3-(2-cyanoacetyl)indole. The corresponding reactions utilizing mixtures of 5-amino-3-methyl-1-phenylpyrazole and 3-(2-cyanoacetyl)indole with three different substituted aryl aldehydes were conducted using microwave irradiation under solvent-free conditions to produce the corresponding 4-aryl-6-(1*H*-indol-3-yl)-3-methyl-1-phenylpyrazolo[3,4-*b*]pyridine- 5-carbonitriles, (I)–(III) (see scheme below).
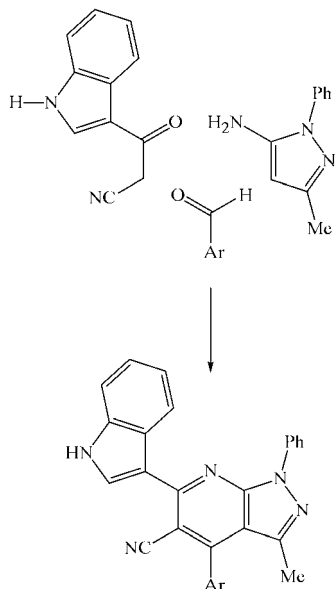
With the exception of the methoxy groups in compounds (II) and (III), the skeletal conformations of the heterocyclic components can be defined in terms of just three torsion angles, which define the orientation of the three cyclic substituents relative to the central pyrazolopyridine unit (Table 1). In each compound, the rotation of the substituents out of the plane of the pyrazolopyridine unit is least for the C11–C16 aryl ring and most for the C41–C46 aryl ring. Simple steric considerations, particularly those involving the methyl and cyano substituents at atoms C3 and C5, account for this order, although not for the detailed differences in the torsion angles.

The methoxy C atom in compound (II) is almost coplanar with the adjacent aryl ring, as are the methoxy atoms C431 and C451 in compound (III); on the other hand, the C44/O44/C441 plane defining the orientation of the central methoxy substituent in compound (III) is at an angle of almost 60° to the adjacent aryl ring. The exocyclic C—C—O bond angles exhibit the usual pattern, with the two values at each substituent differing by almost 10° for the in-plane methoxy groups, while for the out-of-plane methoxy group in compound (III) these angles differ by very much less (Table 1).

In each of the solvates (I) and (II), the molecular components within the selected asymmetric units are linked by an N—H···O hydrogen bond (Table 2), so that the N—H bond is not available for the formation of a hydrogen bond to another

heterocyclic molecule. In compound (I), the heterocyclic components are linked by a C—H···π(arene) hydrogen bond; atom C42 at (x, y, z) acts as a hydrogen-bond donor to the C63A/C64–C67/C67A aryl ring at (1 − x, 1 − y, 1 − z), so
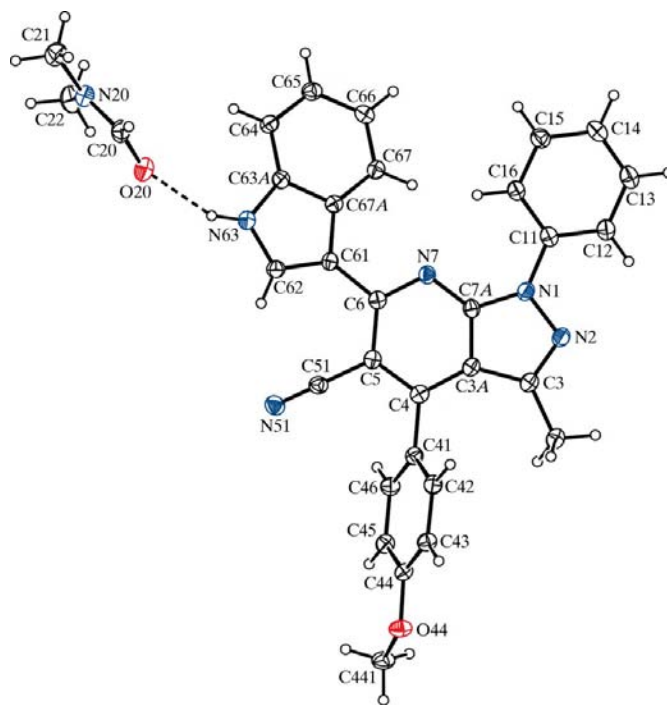
Figure 2
The independent components of (II), showing the atom-labelling scheme and the N—H···O hydrogen bond (dashed line) within the selected asymmetric unit. Displacement ellipsoids are drawn at the 30% probability level.
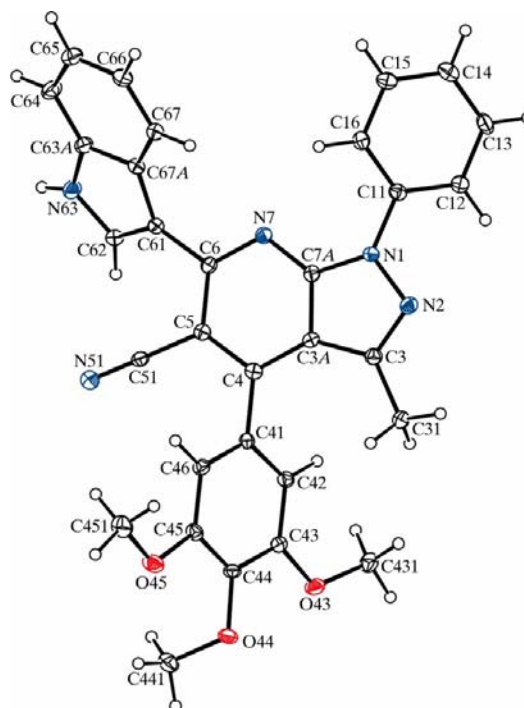
Figure 3
A molecule of (III) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

generating by inversion a cyclic centrosymmetric dimer, centred at $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$ (Fig. 4), from which two dimethylformamide molecules are pendent.

The aggregation of the pyrazolopyridine components in compound (II) utilizes both C—H$\cdots\pi$(arene) and C—H$\cdots$N hydrogen bonds (Table 2). As in compound (I), atom C42 at (x, y, z) acts as a hydrogen-bond donor to the C63A/C64–C67/ C67A aryl ring, now at $(\frac{1}{2} - x, \frac{3}{2} - y, 1 - z)$, so generating by inversion a cyclic centrosymmetric motif. In addition, atom C46 at (x, y, z) acts as a donor to nitrile atom N51 at $(\frac{1}{2} - x, \frac{1}{2} - y, 1 - z)$, thus generating by inversion a centrosymmetric $R_2^2(14)$ (Bernstein *et al.*, 1995) motif. Propagation by inversion of these two hydrogen bonds then generates a chain of rings parallel to [010], with rings containing pairs of C—H$\cdots\pi$(arene) hydrogen bonds centred at $(\frac{1}{4}, n - \frac{1}{4}, \frac{1}{2})$ (where n represents zero or an integer) alternating with rings containing pairs of C—H$\cdots$N hydrogen bonds centred at $(\frac{1}{4}, n + \frac{1}{4}, \frac{1}{2})$
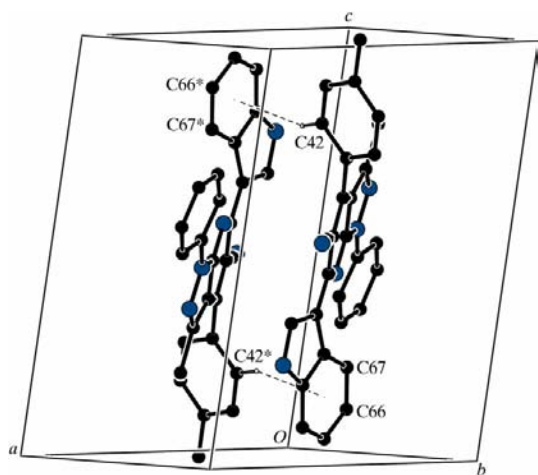

Figure 4
Part of the crystal structure of (I), showing the formation of a centrosymmetric hydrogen-bonded dimer. For the sake of clarity, the solvent molecule and H atoms not involved in the motif shown have been omitted. Atoms marked with an asterisk (*) are at the symmetry position $(1 - x, 1 - y, 1 - z)$.
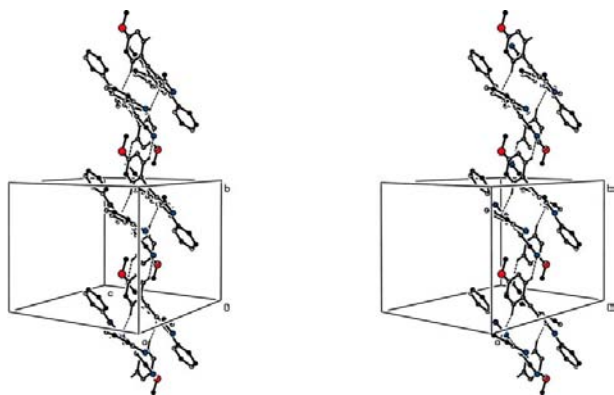

Figure 5
A stereoview of part of the crystal structure of (II), showing the formation of a hydrogen-bonded chain along [010], containing two types of centrosymmetric ring. For the sake of clarity, the solvent molecule and H atoms not involved in the motif shown have been omitted.
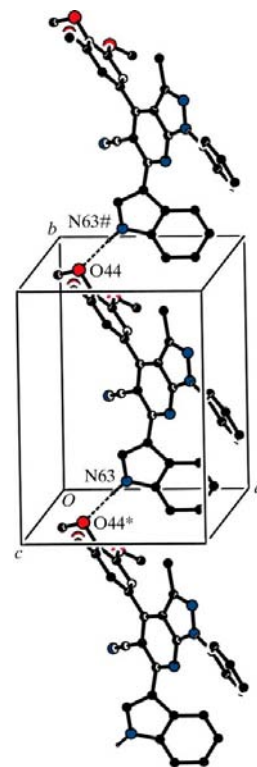

Figure 6
Part of the crystal structure of (III), showing the formation of a hydrogen-bonded $C(12)$ chain along [010]. For the sake of clarity, H atoms not involved in the motif shown have been omitted. Atoms marked with an asterisk (*) or a hash (#) are at the symmetry positions $(x, -1 + y, z)$ and $(x, 1 + y, z)$, respectively.

(where n represents zero or an integer) (Fig. 5). The dimethylformamide solvent molecules are pendent from the chain, linked to it *via* N—H$\cdots$O hydrogen bonds. Four chains of this type pass through each unit cell, but there are no direction-specific interactions between the chains.

In the solvent-free compound (III), the molecules are linked by a single nearly-linear N—H$\cdots$O hydrogen bond, but C—H$\cdots$N and C—H$\cdots\pi$(arene) hydrogen bonds are absent. Atom N63 in the molecule at (x, y, z) acts as a hydrogen-bond donor to the central methoxy atom O44 in the molecule at $(x, -1 + y, z)$, so generating by translation a $C(12)$ chain running parallel to the [010] direction (Fig. 6).

In each compound, there is a rather weak π–π stacking interaction involving the pyridyl rings in pairs of molecules related by inversion. In compounds (I) and (III), the rings involved are at (x, y, z) and $(1 - x, 1 - y, 1 - z)$, while in compound (II), they are at (x, y, z) and $(\frac{1}{2} - x, \frac{3}{2} - y, 1 - z)$. The interplanar spacings in compounds (I), (II) and (III) are 3.632 (2), 3.538 (2) and 3.583 (2) Å, respectively, and the ring-centroid separations are 3.956 (2), 3.815 (2) and 3.831 (2) Å, corresponding to ring-centroid offsets of 1.568 (2), 1.427 (2) and 1.356 (2) Å, respectively. In compounds (I) and (II), the interactions weakly augment the actions of the C—H$\cdots\pi$(arene) hydrogen bonds, while in compound (III), the stacking interactions link, albeit weakly, an antiparallel pair of $C(12)$ chains.

organic compounds

Experimental

Equimolar mixtures (0.5 mmol of each component) of 5-amino-3-methyl-1-phenylpyrazole, 3-(2-cyanoacetyl)indole and the appropriate aldehyde [4-methylbenzaldehyde for (I), 4-methoxybenzaldehyde for (II) and 3,4,5-trimethoxybenzaldehyde for (III)] were subjected to microwave irradiation in the absence of solvent (maximum power 300 W during 9 min at a controlled temperature of 473 K) using a focused microwave reactor (CEM Discover). The resulting reaction mixtures were then extracted with hot ethanol/dimethylformamide mixtures (2:1 v/v); the solid products were collected by filtration and washed successively with ethanol and diethyl ether to yield crystals of compounds (I)–(III) suitable for single-crystal X-ray diffraction. Compound (I): yield 89%, m.p. 547 K; MS (70 eV) m/z (%) = 439 (100, M^+), 424 (37), 397 (6), 77 (40), 51 (30). Compound (II): yield 85%, m.p. 543 K; MS (70 eV) m/z (%) = 455 (100, M^+), 424 (9), 409 (6), 77 (8). Compound (III): yield 88%, m.p. 548 K; MS (70 eV) m/z (%) = 515 (100, M^+), 484 (23), 414 (8), 258 (10), 77 (31), 51 (13).

Compound (I)

Crystal data

$C_{29}H_{21}N_5 \cdot C_3H_7NO$	$\gamma = 96.171\ (3)°$
$M_r = 512.60$	$V = 1312.2\ (2)$ Å^3
Triclinic, $P\bar{1}$	$Z = 2$
$a = 9.8060\ (3)$ Å	Mo $K\alpha$ radiation
$b = 10.1820\ (3)$ Å	$\mu = 0.08$ mm^{-1}
$c = 13.818\ (2)$ Å	$T = 120\ (2)$ K
$\alpha = 97.035\ (6)°$	$0.40 \times 0.18 \times 0.18$ mm
$\beta = 104.455\ (6)°$	

Data collection

Bruker–Nonius KappaCCD diffractometer	31081 measured reflections
Absorption correction: multi-scan ($SADABS$; Sheldrick, 2003)	5996 independent reflections
	3816 reflections with $I > 2\sigma(I)$
$T_{min} = 0.961$, $T_{max} = 0.985$	$R_{int} = 0.048$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.050$	356 parameters
$wR(F^2) = 0.146$	H-atom parameters constrained
$S = 1.06$	$\Delta\rho_{max} = 0.37$ e Å^{-3}
5996 reflections	$\Delta\rho_{min} = -0.31$ e Å^{-3}

Compound (II)

Crystal data

$C_{29}H_{21}N_5O \cdot C_3H_7NO$	$V = 5279.5\ (12)$ Å^3
$M_r = 528.60$	$Z = 8$
Monoclinic, $C2/c$	Mo $K\alpha$ radiation
$a = 30.303\ (3)$ Å	$\mu = 0.09$ mm^{-1}
$b = 11.3490\ (16)$ Å	$T = 120\ (2)$ K
$c = 20.344\ (3)$ Å	$0.51 \times 0.49 \times 0.27$ mm
$\beta = 131.010\ (5)°$	

Data collection

Bruker–Nonius KappaCCD diffractometer	63662 measured reflections
Absorption correction: multi-scan ($SADABS$; Sheldrick, 2003)	6055 independent reflections
	3416 reflections with $I > 2\sigma(I)$
$T_{min} = 0.949$, $T_{max} = 0.977$	$R_{int} = 0.074$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.069$	365 parameters
$wR(F^2) = 0.237$	H-atom parameters constrained
$S = 1.07$	$\Delta\rho_{max} = 0.43$ e Å^{-3}
6055 reflections	$\Delta\rho_{min} = -0.34$ e Å^{-3}

Compound (III)

Crystal data

$C_{31}H_{25}N_5O_3$	$\gamma = 90.994\ (7)°$
$M_r = 515.56$	$V = 1272.3\ (3)$ Å^3
Triclinic, $P\bar{1}$	$Z = 2$
$a = 8.8241\ (10)$ Å	Mo $K\alpha$ radiation
$b = 11.9901\ (9)$ Å	$\mu = 0.09$ mm^{-1}
$c = 12.9130\ (17)$ Å	$T = 120\ (2)$ K
$\alpha = 99.372\ (9)°$	$0.38 \times 0.20 \times 0.18$ mm
$\beta = 108.822\ (12)°$	

Data collection

Bruker–Nonius KappaCCD diffractometer	31225 measured reflections
Absorption correction: multi-scan ($SADABS$; Sheldrick, 2003)	5825 independent reflections
	3165 reflections with $I > 2\sigma(I)$
$T_{min} = 0.960$, $T_{max} = 0.984$	$R_{int} = 0.075$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.055$	356 parameters
$wR(F^2) = 0.152$	H-atom parameters constrained
$S = 1.06$	$\Delta\rho_{max} = 0.27$ e Å^{-3}
5825 reflections	$\Delta\rho_{min} = -0.35$ e Å^{-3}

Table 1
Selected torsion and bond angles (°) for compounds (I)–(III).

	(I)	(II)	(III)
N2—N1—C11—C12	9.5 (3)	13.1 (4)	34.4 (3)
C3A—C4—C41—C42	57.4 (3)	61.4 (4)	−56.7 (3)
C5—C6—C61—C62	29.3 (3)	28.6 (4)	−45.3 (3)
C42—C43—O43—C431	–	–	9.0 (3)
C43—C44—O44—C441	–	−172.3 (2)	−119.0 (2)
C46—C45—O45—C451	–	–	−9.7 (3)
C42—C43—O43	–	–	124.6 (2)
C44—C43—O43	–	–	115.29 (19)
C43—C44—O44	–	116.0 (2)	118.7 (2)
C45—C44—O44	–	124.3 (3)	121.3 (2)
C44—C45—O45	–	–	115.25 (19)
C46—-C45—O45	–	–	124.4 (2)
C43—O43—C431	–	–	117.41 (17)
C44—O44—C441	–	116.3 (2)	115.08 (17)
C45—O45—C451	–	–	117.26 (18)

Table 2
Hydrogen-bond parameters (Å, °) for compounds (I)–(III).

Cg represents the centroid of the C63A/C64–C67/C67A ring.

Compound	$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
(I)	N63—H63$\cdots$O20	0.88	1.89	2.767 (2)	173
	C42—H42$\cdots$$Cg^i$	0.95	2.65	3.514 (3)	151
(II)	N63—H63$\cdots$O20	0.88	1.96	2.757 (5)	149
	C42—H42$\cdots$$Cg^{ii}$	0.95	2.68	3.558 (3)	154
	C46—H46$\cdots$N51^{iii}	0.95	2.43	3.213 (4)	140
(III)	N63—H63$\cdots$O44^{iv}	0.88	2.06	2.939 (2)	173

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $-x+\frac{1}{2}, -y+\frac{3}{2}, -z+1$; (iii) $-x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (iv) $x, -1+y, z$.

Crystals of compounds (I) and (III) are triclinic; for each compound, space group $P\bar{1}$ was selected and confirmed by the structure analysis. For compound (II), the systematic absences permitted $C2/c$ and Cc as possible space groups; $C2/c$ was selected and confirmed by the structure analysis. All H atoms were located in difference maps, and then treated as riding atoms, with C—H =

0.95 (aromatic and formyl) or 0.98 Å (methyl) and N—H = 0.88 Å, and with $U_{iso}(H) = kU_{eq}$(carrier), where $k = 1.5$ for the methyl groups and $k = 1.2$ for all other H atoms.

For all compounds, 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: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *OSCAIL* (McArdle, 2003) and *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* and *PRPKAPPA* (Ferguson, 1999).

References

Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.

Burla, M. C., Caliandro, R., Camalli, M., Carrozzini, B., Cascarano, G. L., De Caro, L., Giacovazzo, C., Polidori, G. & Spagna, R. (2005). *J. Appl. Cryst.* **38**, 381–388.

Duisenberg, A. J. M., Hooft, R. W. W., Schreurs, A. M. M. & Kroon, J. (2000). *J. Appl. Cryst.* **33**, 893–898.

Duisenberg, A. J. M., Kroon-Batenburg, L. M. J. & Schreurs, A. M. M. (2003). *J. Appl. Cryst.* **36**, 220–229.

Ferguson, G. (1999). *PRPKAPPA*. University of Guelph, Canada.

Hooft, R. W. W. (1999). *COLLECT*. Nonius BV, Delft, The Netherlands.

McArdle, P. (2003). *OSCAIL for Windows*. Version 10. Crystallography Centre, Chemistry Department, NUI Galway, Ireland.

Quiroga, J., Portilla, J., Serrano, H., Abonía, R., Insuasty, B., Nogueras, M. & Cobo, J. (2007). *Tetrahedron*, **48**, 1987–1990.

Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.

Sheldrick, G. M. (2003). *SADABS*. Version 2.10. University of Göttingen, Germany.

Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.