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An analysis of C—H···O and C—H···π interactions in three substituted 4-ketotetrahydroindoles

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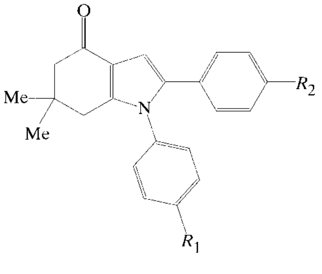
The crystal and molecular structures of the three 4-ketotetrahydroindoles 2-(4-chlorophenyl)-1-(4-fluorophenyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indol-4-one ($C_{22}H_{19}ClFNO$), (I), 1-(4-fluorophenyl)-2-(4-methoxyphenyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indol-4-one ($C_{23}H_{22}FNO_2$), (II), and 6,6-dimethyl-1,2-diphenyl-4,5,6,7-tetrahydro-1*H*-indol-4-one ($C_{22}H_{21}NO$), (III), have been determined *via* single-crystal X-ray diffraction in order to study the intermolecular interactions therein. All three structures are stabilized *via* intermolecular C—H···O and C—H···π interactions, generating different molecular motifs.

Comment

The generation of different types of packing motifs in crystalline lattices has been illustrated in detail in the literature. Different types of intermolecular interactions, such as hydrogen bonding (Desiraju, 1989, 2000, 2002; Aakeröy, 1997; Guru Row, 1999; Hunter *et al.*, 2001), C—H···π interactions (Nishio *et al.*, 1995; Umezawa *et al.*, 1999; Takahashi *et al.*, 2000), π–π stacking (Hunter, 1993, 1994) and C—H···O hydrogen bonding (Desiraju & Steiner, 1999; Steiner, 2002) have been reviewed extensively. Recently, it has been shown that 'organic fluorine' provides similar interactions, generating packing motifs in the presence or absence of other intermolecular forces (Prasanna & Guru Row, 2000*a*,*b*,*c*, 2001). We have been interested in the study of the role of organic fluorine in the packing of organic molecules which show biological activity (Choudhury, Urs, Guru Row & Nagarajan, 2002; Choudhury, Urs, Smith *et al.*, 2002). Against this background, we report here the crystal and molecular structures of 2-(4-chlorophenyl)-1-(4-fluorophenyl)-, (I), and 1-(4-fluorophenyl)-2-(4-methoxyphenyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indol-4-one, (II), and compare these with the corresponding unsubstituted compound 6,6-dimethyl-1,2-diphenyl-4,5,6,7-tetrahydro-1*H*-indol-4-one, (III) (Varghese *et al.*, 1986), the structure of which we have redetermined.



(I) R_1=F, R_2=Cl
(II) R_1=F, R_2=OMe
(III) R_1=R_2=H

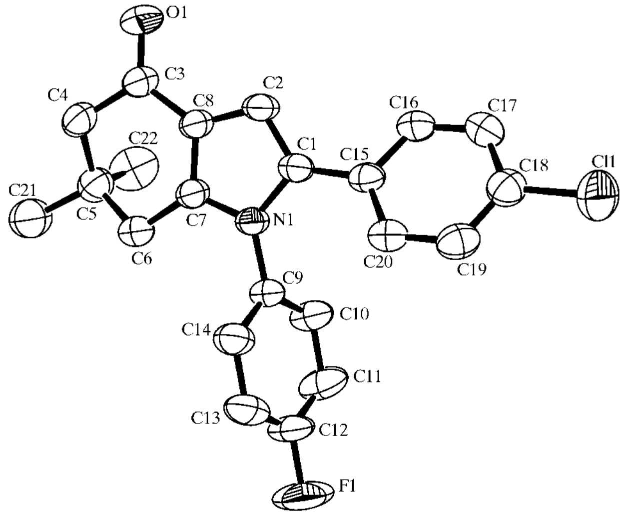


Figure 1
A view of the molecule of (I), showing the atom-numbering scheme and displacement ellipsoids drawn at the 50% probability level. H atoms have been omitted for clarity.

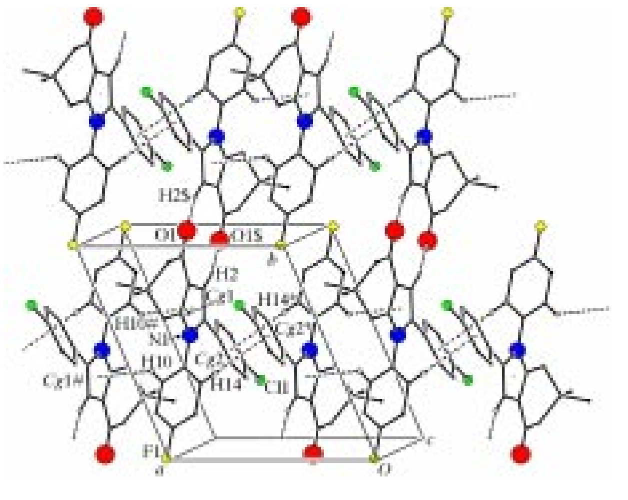


Figure 2
A packing diagram for (I), showing the C—H···O hydrogen-bonded dimer and the intermolecular C—H···π interaction. *Cg*1 is the centroid of the five-membered N1/C1/C2/C8/C7 ring and *Cg*2 is the centroid of the C9–C14 phenyl ring. Atoms labelled with a dollar sign ($), hash (#) or asterisk (*) are at symmetry positions (1 − *x*, 2 − *y*, 1 − *z*), (2 − *x*, 1 − *y*, 1 − *z*) and (1 − *x*, 1 − *y*, 1 − *z*), respectively.

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Most unsubstituted 4-ketotetrahydroindoles have been found to be biologically inactive (Remers *et al.*, 1971) and this inactivity was attributed to the extended conjugation of the C═O group with the indole N atom (Weiss *et al.*, 1968). In order to delocalize the lone pair of electrons on N and to facilitate the activity of the keto function, a series of 1,2-diaryl derivatives was synthesized (Nagarajan *et al.*, 1985). It was found that differently substituted phenyl groups on the 1- or 2-positions facilitate biological activity. Compound (I) of the present study was inactive, whereas (II) showed considerable activity, as reported by Nagarajan *et al.* (1985). We have redetermined the structure of the unsubstituted compound, (III), since the intermolecular interactions were not discussed in detail in the earlier report of Varghese *et al.* (1986).

In compound (I), the six-membered ring of the tetrahydroindole system (Fig. 1) has an envelope conformation, with atom C5 a distance of −0.641 (3) Å from the C3/C4/C6/C7/C8 plane. Selected torsion angles are given in Table 1. The dihedral angle between the 4-fluorophenyl and 4-chlorophenyl rings is 69.84 (7)°. The packing of the molecules in the crystal lattice (Fig. 2) is stabilized *via* C—H···O and C—H···π interactions (Table 2). There are two independent C—H···π interactions, which link the molecules in the *b* direction. Thus, molecules packed around the inversion centres at $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$ and $(1, \frac{1}{2}, \frac{1}{2})$ are linked by pairs of independent C—H···π interactions. C—H···O interactions about the inversion centre at $(\frac{1}{2}, 1, \frac{1}{2})$ then serve to link these chains to form sheets of molecules in the *bc* plane. It is of interest to note that there are no interactions involving the halogen atoms, though the structure contains Cl as well as F.

In compound (II), the six-membered ring of the tetrahydroindole system (Fig. 3) also has an envelope conformation, with atom C5 a distance of −0.618 (2) Å from the C3/C4/C6/C7/C8 plane, similar to what was observed for (I). Selected torsion angles are given in Table 3. The dihedral angle between the 4-fluorophenyl and 4-methoxyphenyl rings is 60.94 (4)°. The molecules pack in the unit cell (Fig. 4) *via* two different C—H···O interactions (Table 4) in the $(10\overline{1})$ plane,

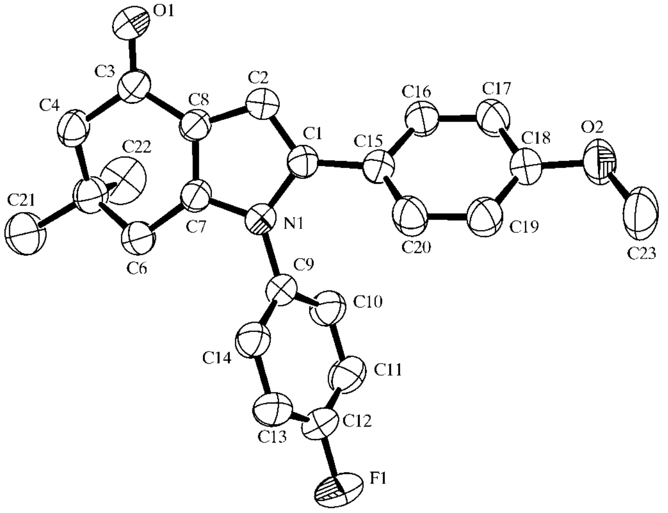

Figure 3
A view of the molecule of (II), showing the atom-numbering scheme and displacement ellipsoids drawn at the 50% probability level. H atoms have been omitted for clarity.

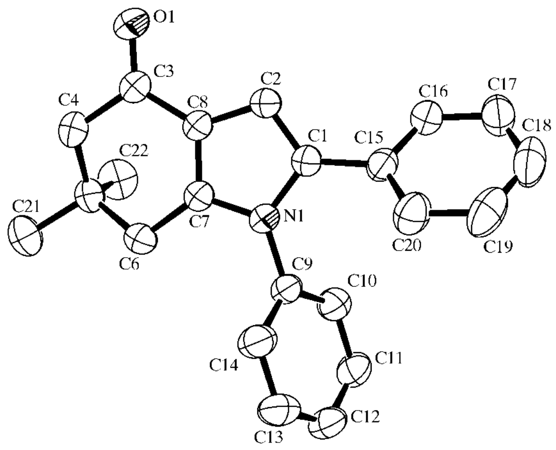

Figure 5
A view of the molecule of (III), showing the atom-numbering scheme and displacement ellipsoids drawn at the 50% probability level. H atoms have been omitted for clarity.

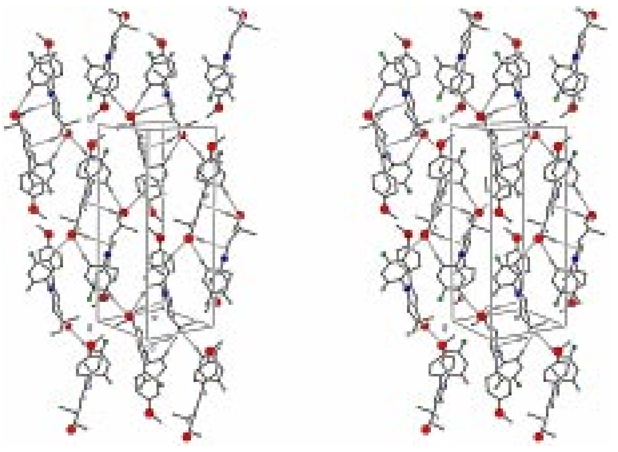

Figure 4
A stereoview of the packing of (II), showing the C—H···O hydrogen-bonded sheet motif and C—H···π interactions.

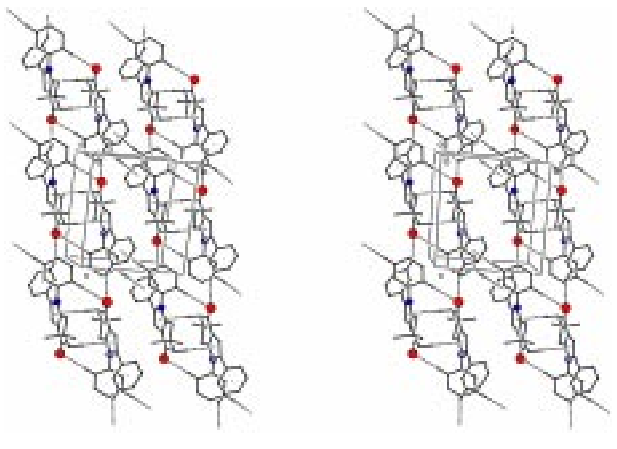

Figure 6
A stereoview of the packing of (III), showing the C—H···O hydrogen-bonded ladder motif and C—H···π interactions

generating a sheet structure. This is further stabilized by an additional C—H$\cdots\pi$ interaction, which reinforces the two-dimensional sheet (Fig. 4). Once again, it is to be noted that the F atom does not generate any significant interaction.

In compound (III), the six-membered ring of the tetrahydroindole system (Fig. 5) again has an envelope conformation, with atom C5 a distance of −0.632 (2) Å from the C3/C4/C6/C7/C8 plane. Selected torsion angles are given in Table 5. The dihedral angle between the phenyl rings is 62.99 (6)°. The variation in dihedral angles in (I), (II) and (III) clearly shows that the conformations of the molecules are significantly different among the three compounds. The molecules of (III) pack in the unit cell *via* two different C—H$\cdots$O interactions (Fig. 6 and Table 6), generating a 'ladder' motif which is further reinforced by a C—H$\cdots\pi$ interaction involving C4—H4*B* (Table 6). These ladders are then linked to form a two-dimensional sheet in the (101) plane *via* a further C—H$\cdots\pi$ interaction involving C11—H11 and the centroid of the C9–C14 phenyl ring (*Cg*2) at $(-x, 1-y, 2-z)$.

These three structures illustrate the co-existence of C—H$\cdots$O and C—H$\cdots\pi$ interactions and their ability to generate different packing motifs with altered molecular conformations. Such subtle variations might have a significant impact on the biological activities of such compounds. Indeed, only compound (II) is found to be biologically active.

Experimental

Compounds (I)–(III) were synthesized according to the procedure of Nagarajan *et al.* (1985). Single crystals suitable for X-ray diffraction studies were grown from solutions in acetone (analytical reagent) by slow evaporation at 283 K.

Compound (I)

Crystal data

$C_{22}H_{19}ClFNO$
$M_r = 367.83$
Triclinic, $P\overline{1}$
$a = 9.246$ (3) Å
$b = 10.228$ (4) Å
$c = 11.177$ (4) Å
$\alpha = 80.529$ (6)°
$\beta = 86.335$ (7)°
$\gamma = 65.120$ (6)°
$V = 945.7$ (6) Å^3
$Z = 2$
$D_x = 1.292$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2435 reflections
$\theta = 2.3$–21.2°
$\mu = 0.22$ mm^{-1}
$T = 293$ (2) K
Plate, colourless
0.50 × 0.30 × 0.20 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996)
$T_{\min} = 0.844$, $T_{\max} = 0.957$
9987 measured reflections
3788 independent reflections
2811 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.024$
$\theta_{\max} = 26.4°$
$h = -11 \rightarrow 11$
$k = -12 \rightarrow 12$
$l = -13 \rightarrow 13$

Refinement

Refinement on F^2
$R(F) = 0.050$
$wR(F^2) = 0.118$
$S = 1.04$
3788 reflections
311 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0455P)^2 + 0.2584P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.20$ e Å^{-3}
$\Delta\rho_{\min} = -0.22$ e Å^{-3}

Table 1
Selected torsion angles (°) for (I).

C9—N1—C1—C15	−3.7 (3)	C5—C6—C7—C8	20.6 (3)
O1—C3—C4—C5	145.5 (2)	C6—C7—C8—C3	1.4 (3)
C8—C3—C4—C5	−36.3 (3)	C4—C3—C8—C7	6.1 (3)
C3—C4—C5—C6	57.3 (3)	C7—N1—C9—C10	106.0 (2)
C4—C5—C6—C7	−47.0 (2)	N1—C1—C15—C16	148.67 (18)
C9—N1—C7—C8	−177.68 (16)		

Table 2
Hydrogen-bonding geometry (Å, °) for (I).

*Cg*1 is the centroid of the five-membered N1/C1/C2/C8/C7 ring and *Cg*2 is the centroid of the C9–C14 phenyl ring.

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
C2—H2$\cdots$O1$^{\rm i}$	0.90 (2)	2.50 (2)	3.358 (3)	158 (2)
C10—H10$\cdots$*Cg*1$^{\rm ii}$	0.96 (2)	2.93	3.723 (3)	142
C14—H14$\cdots$*Cg*2$^{\rm iii}$	0.94 (2)	2.90	3.804 (3)	162

Symmetry codes: (i) $1-x, 2-y, 1-z$; (ii) $2-x, 1-y, 1-z$; (iii) $1-x, 1-y, 1-z$.

Compound (II)

Crystal data

$C_{23}H_{22}FNO_2$
$M_r = 363.42$
Monoclinic, $P2_1/n$
$a = 10.112$ (2) Å
$b = 19.073$ (4) Å
$c = 11.287$ (3) Å
$\beta = 116.348$ (3)°
$V = 1950.8$ (8) Å^3
$Z = 4$
$D_x = 1.237$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 974 reflections
$\theta = 2.7$–24.3°
$\mu = 0.09$ mm^{-1}
$T = 293$ (2) K
Prism, colourless
0.40 × 0.30 × 0.20 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
$T_{\min} = 0.887$, $T_{\max} = 0.983$
14 313 measured reflections
3562 independent reflections
2818 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.024$
$\theta_{\max} = 25.4°$
$h = -12 \rightarrow 12$
$k = -22 \rightarrow 21$
$l = -13 \rightarrow 13$

Table 3
Selected torsion angles (°) for (II).

C9—N1—C1—C15	0.7 (2)	C5—C6—C7—C8	22.9 (2)
O1—C3—C4—C5	151.96 (15)	C6—C7—C8—C3	1.0 (2)
C8—C3—C4—C5	−29.9 (2)	C4—C3—C8—C7	1.9 (2)
C3—C4—C5—C6	53.03 (19)	C7—N1—C9—C10	112.95 (17)
C4—C5—C6—C7	−46.9 (2)	N1—C1—C15—C16	136.24 (16)
C9—N1—C7—C8	−178.73 (13)		

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

*Cg*1 is the centroid of the five-membered N1/C1/C2/C8/C7 ring.

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
C11—H11$\cdots$O1$^{\rm i}$	0.97 (2)	2.41 (2)	3.366 (2)	169 (1)
C14—H14$\cdots$O1$^{\rm ii}$	0.96 (2)	2.48 (2)	3.428 (2)	173 (1)
C4—H4*B*$\cdots$*Cg*1$^{\rm ii}$	1.00 (2)	2.69	3.606 (2)	166

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

Acta Cryst. (2004). C**60**, o219–o222 A. R Choudhury *et al.* • $C_{22}H_{19}ClFNO$, $C_{23}H_{22}FNO_2$ and $C_{22}H_{21}NO$ **o221**

Table 5
Selected torsion angles (°) for (III).

C9—N1—C1—C15	−5.4 (2)	C5—C6—C7—C8	20.6 (2)
O1—C3—C4—C5	152.69 (14)	C6—C7—C8—C3	4.3 (2)
C8—C3—C4—C5	−29.93 (19)	C4—C3—C8—C7	0.08 (19)
C3—C4—C5—C6	53.75 (17)	C7—N1—C9—C10	115.85 (15)
C4—C5—C6—C7	−46.84 (17)	N1—C1—C15—C16	137.79 (15)
C9—N1—C7—C8	−176.85 (11)		

Refinement

Refinement on F^2
$R(F) = 0.041$
$wR(F^2) = 0.106$
$S = 1.04$
3562 reflections
332 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0502P)^2 + 0.3423P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.15$ e Å^{-3}
$\Delta\rho_{\min} = -0.19$ e Å^{-3}

Table 6
Hydrogen-bonding geometry (Å, °) for (III).

*Cg*1 is the centroid of the five-membered N1/C1/C2/C8/C7 ring and *Cg*2 is the centroid of the C9–C14 phenyl ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C14—H14···O1^{i}	0.97 (2)	2.57 (2)	3.533 (3)	173 (1)
C19—H19···O1^{ii}	0.93 (2)	2.58 (2)	3.389 (3)	145 (2)
C4—H4*B*···*Cg*1^{i}	0.99 (2)	2.74	3.723 (3)	172
C11—H11···*Cg*2^{iii}	0.97 (2)	2.75	3.620 (3)	149

Symmetry codes: (i) $1-x, -y, 1-z$; (ii) $x-1, y, 1+z$; (iii) $-x, 1-y, 2-z$.

Compound (III)

Crystal data

$C_{22}H_{21}NO$
$M_r = 315.40$
Triclinic, $P\overline{1}$
$a = 9.315$ (5) Å
$b = 9.793$ (5) Å
$c = 11.048$ (6) Å
$\alpha = 81.362$ (9)°
$\beta = 65.691$ (7)°
$\gamma = 77.999$ (8)°
$V = 896.0$ (8) Å^3
$Z = 2$
$D_x = 1.169$ Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 985 reflections
$\theta = 2.4$–24.2°
$\mu = 0.07$ mm^{-1}
$T = 293$ (2) K
Block, colourless
0.35 × 0.30 × 0.20 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
$T_{\min} = 0.946$, $T_{\max} = 0.986$
7395 measured reflections
3259 independent reflections
2604 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.014$
$\theta_{\max} = 25.4°$
$h = -11 \rightarrow 11$
$k = -11 \rightarrow 11$
$l = -12 \rightarrow 13$

Refinement

Refinement on F^2
$R(F) = 0.040$
$wR(F^2) = 0.104$
$S = 1.04$
3259 reflections
301 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0528P)^2 + 0.121P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.13$ e Å^{-3}
$\Delta\rho_{\min} = -0.17$ e Å^{-3}

The ranges of the C—H bond lengths in (I), (II) and (III) are 0.91 (3)–1.08 (3), 0.93 (2)–1.01 (3) and 0.93 (2)–1.05 (2) Å, respectively.

For all three title compounds, data collection: *SMART* (Bruker, 2000); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2000); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997), *CAMERON* (Watkin *et al.*, 1993) and *PLATON* (Spek, 2003); software used to prepare material for publication: *WinGX* (Farrugia, 1999) and *PLATON*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1731). Services for accessing these data are described at the back of the journal.

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