

Two 1,4-dihydropyridine derivatives with potential calcium-channel antagonist activity

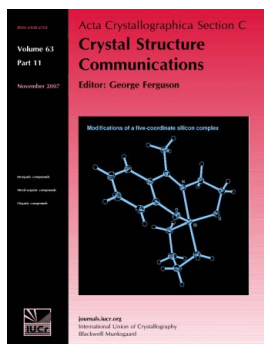
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Two 1,4-dihydropyridine derivatives
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antagonist activityAnthony Linden,^{a*} Cihat Şafak,^b Rahime Şimşek^b and
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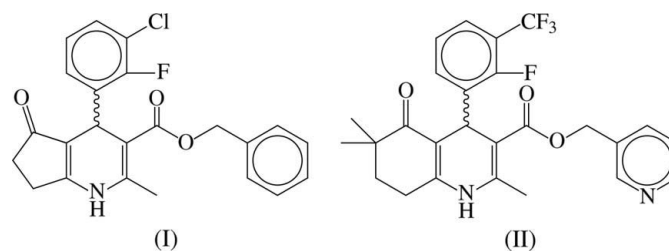
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The title compounds, benzyl 4-(3-chloro-2-fluorophenyl)-2-methyl-5-oxo-4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxylate, $C_{23}H_{19}ClFNO_3$, (I), and 3-pyridylmethyl 4-[2-fluoro-3-(trifluoromethyl)phenyl]-2,6,6-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, $C_{26}H_{24}F_4N_2O_3$, (II), belong to a class of 1,4-dihydropyridines whose members sometimes display calcium modulatory properties. The 1,4-dihydropyridine ring in each structure has a shallower than usual shallow-boat conformation and is nearly planar in (I). In each structure, the halogen-substituted benzene ring is oriented such that the halogen substituents are in a synperiplanar orientation with respect to the 1,4-dihydropyridine ring plane. The oxocyclopentene ring in (I) is planar, while the oxocyclohexene ring in (II) has a half-chair conformation, which is less commonly observed than the envelope conformation usually found in related compounds. In (I), the frequently observed intermolecular $N-H\cdots O$ hydrogen bond between the amine group and the carbonyl O atom of the oxocyclopentene ring of a neighbouring molecule links the molecules into extended chains; there are no other significant intermolecular interactions. By contrast, the amine group in (II) forms an $N-H\cdots N$ hydrogen bond with the pyridine ring N atom of a neighbouring molecule. Additional $C-H\cdots O$ interactions complete a two-dimensional hydrogen-bonded network. The halogen-substituted benzene ring has a weak intramolecular $\pi-\pi$ interaction with the pyridine ring. A stronger $\pi-\pi$ interaction occurs between the 1,4-dihydropyridine rings of centrosymmetrically related molecules.

Comment

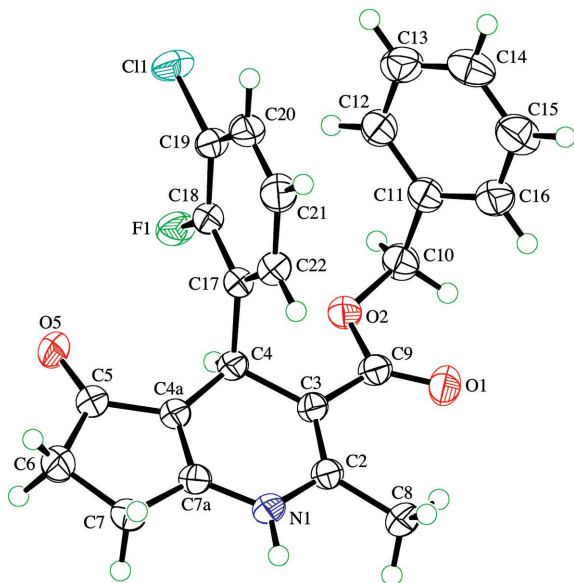
Cardiovascular diseases include disorders of the heart and blood vessels, hypertension, peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure. Calcium-channel antagonists inhibit muscle contraction by

blocking the influx of Ca^{2+} through calcium channels and are used as anti-anginal and antihypertensive drugs (Triggle & Swamy, 1980; Janis & Triggle, 1984). 1,4-Dihydropyridine (1,4-DHP) derivatives are the most studied group and nifedipine is the prototype of calcium-channel antagonists (Triggle, 1990, 2003; Şafak & Şimşek, 2006; Bülbül *et al.*, 2009). Modifications to the nifedipine structure, such as replacing the ester moiety with various acyl analogues or fusing one of the carbonyl groups into the ring system, produces some active molecules (Şimşek *et al.*, 2006; Gündüz *et al.*, 2009). Following on from these structure–activity relationship studies and our experience in this area, we synthesized benzyl 4-(3-chloro-2-fluorophenyl)-2-methyl-5-oxo-4,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxylate, (I), and 3-pyridylmethyl 4-[2-fluoro-3-(trifluoromethyl)phenyl]-2,6,6-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, (II). Compound (I) shows calcium-channel blocker activity in isolated rat ileum and rat thoracic artery. Compound (II) also demonstrates calcium-channel blocker activity. The maximum relaxant responses (E_{max}) and pD_2 values of (II) were determined on isolated strips of rabbit gastric fundus smooth muscle (Şafak, 2010).

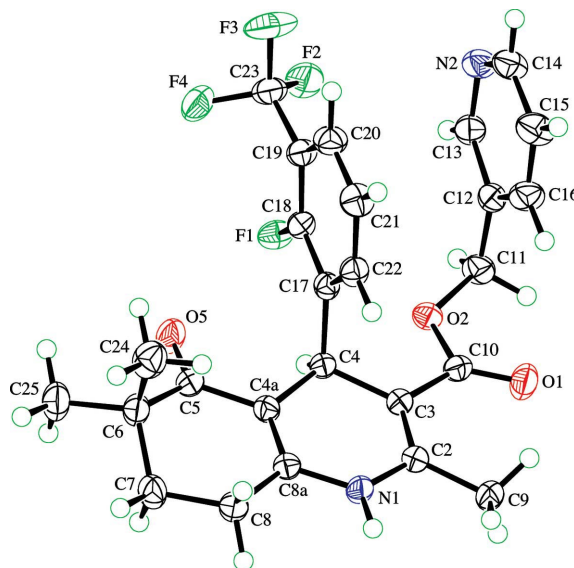


Views of the asymmetric units of the structures of (I) and (II) are shown in Figs. 1 and 2, respectively. Most of the bond lengths and angles in (I) and (II) have normal values. There are small angular distortions about atom C2 and the ester C atom [C9 in (I) and C10 in (II)] (Tables 1 and 3), which result from steric interactions between the methyl substituent at C2 and atom O1 of the ester substituent at C3 [$O1\cdots C8$ in (I) and $O1\cdots C9$ in (II) are both 2.847 (2) Å]. The presence of π -electron conjugation keeps the ester group at C3 almost coplanar with the endocyclic double bond [$C2=C3-C9=O1 = -11.3 (3)^\circ$ for (I) and $C2=C3-C10=O1 = -5.6 (3)^\circ$ for (II)] and prevents the ester group from rotating into a sterically more amenable orientation. These properties are consistent with those of related compounds (Linden *et al.*, 2005, 2006).

The 1,4-DHP rings in (I) and (II) have very shallow boat conformations. In (I), the ring is almost completely planar, with atoms N1 and C4 lying just 0.0342 (18) and 0.0612 (19) Å, respectively, from the plane defined by atoms C2/C3/C4a/C7a. The corresponding displacements in (II) are 0.0296 (14) and 0.1004 (16) Å, respectively [atom C8a is in the position represented by C7a in (I)]. The conformations of 4-aryl-1,4-DHP rings have been discussed previously (Goldmann & Stoltefuss, 1991; Linden *et al.*, 1998, 2002, 2005; Şimşek *et al.*, 2000) and it is usual for the ring to have a shallow-boat conformation, although considerable variation in the shal-

**Figure 1**

A view of the molecule of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

**Figure 2**

A view of the molecule of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

lowness of the boat is evident. The displacement of atom C4 from the base of the boat in 1,4-DHP rings is frequently found to be around 0.30 Å (Şimşek *et al.*, 2000). The deviations shown by atom N1 are generally smaller and spread fairly evenly over the range 0.00–0.19 Å (Şimşek *et al.*, 2000; Linden *et al.*, 2002). The deviations shown by atoms N1 in (I) and (II) fall well within this range, while those of C4 show that the C4 end of the boat is much flatter than normal. A completely planar 1,4-DHP ring was found in the structure of *N,N*-diethyl-2,6,6-trimethyl-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide (Linden *et al.*, 2002).

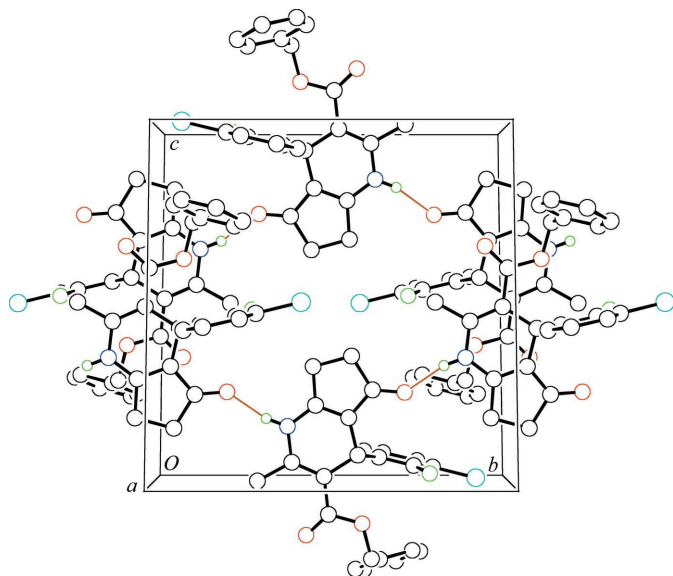
Another measure of the planarity of 1,4-DHP rings is the sum of the magnitudes of the six intraring torsion angles, P , around the ring (Fossheim *et al.*, 1988). For (I) and (II), the values of P are 20.0 (7) and 25.2 (7)°, respectively, which demonstrates that the boat conformations are indeed quite shallow. A mean value of 77 (2)° was found previously for 1,4-DHP rings (Linden *et al.*, 2002), although the P values generally vary over a wide range from 4 to 130°. For nifedipine itself, P is 72° (Miyamae *et al.*, 1986).

The planes of the 3-chloro-2-fluorophenyl ring in (I) and the 2-fluoro-3-(trifluoromethyl)phenyl ring in (II) lie in the usual synperiplanar orientation, which places the benzene-ring substituents above the C4–H bond rather than over the 1,4-DHP ring, which, because of the substituent in the 2-position of the phenyl ring, would be sterically unfavourable. The N1...C4–C17–C22 torsion angles are 10.9 (2) and 5.8 (2)° for (I) and (II), respectively. The corresponding torsion angles in related structures are clustered around 0° and rarely exceed $\pm 30^\circ$ (Linden *et al.*, 2002). The observed orientation of the halophenyl ring brings the C22–H22 bond over the centre of the 1,4-DHP ring, and the distance from atom H22 to the centroid of the 1,4-DHP ring is just 2.81 Å in (I) and 2.67 Å in (II). The shorter distance for the latter is a consequence of the slightly deeper boat conformation of the 1,4-DHP ring, which

raises the halophenyl ring up higher and thereby points the C22–H22 bond more deeply into the centre of the 1,4-DHP ring.

The oxocyclopentene ring in (I) is almost planar, with a maximum deviation from the mean plane defined by the five ring atoms of 0.0292 (19) Å for atom C7a. The angle between the plane defined by the base of the 1,4-DHP ring boat (atoms C2/C3/C4a/C7a) and that of the oxocyclopentene ring is 5.05 (12)°, which indicates that the fused rings are essentially coplanar. The oxocyclohexene ring in (II) adopts a nearly ideal half-chair conformation twisted on the C6–C7 bond, with atoms C6 and C7 lying 0.289 (2) and 0.382 (2) Å, respectively, from the plane defined by the remaining four ring atoms, *viz.* C4a/C5/C8/C8a. The ring-puckering parameters (Cremer & Pople, 1975) for this ring are $Q = 0.4370$ (19) Å, $\theta = 130.1$ (2)° and $\varphi_2 = 335.1$ (3)° for the atom sequence C4a–C5–C6–C7–C8–C8a. The ideal values for a half-chair conformation in a six-membered ring are $\theta = 50^\circ$ (or $180 - 50 = 130^\circ$) and $\varphi_2 = (n \times 60) + 30^\circ$, where n is an integer. Atom C7 of the ring flips down on the opposite side of the oxocyclohexene ring plane to the 2-fluoro-3-(trifluoromethyl)phenyl ring substituent of the adjacent 1,4-DHP ring. A half-chair conformation was also observed in the structure of methyl 4-(2,4-chlorophenyl)-2-methyl-7-phenyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate monohydrate (Linden *et al.*, 2006). More frequently, the oxocyclohexene ring in similar structures involving the 5-oxoquinoline or 1,8-dioxoacridine fragment adopts an envelope conformation, with atom C7 always being the out-of-plane atom, and the side of the oxocyclohexene ring to which C7 deviates is, in the majority, but not all, of these structures, opposite to that in (I) (Linden *et al.*, 2002, 2005).

The angle between the plane of the 3-chloro-2-fluorophenyl ring and that of the phenyl ring of the ester substituent in (I) is 32.65 (10)°, which precludes any chance of there being a π – π

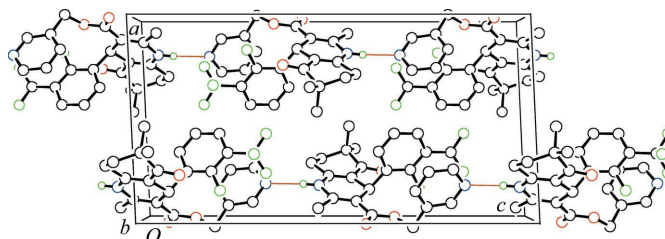
**Figure 3**

A view, down the *a* axis, of the crystal packing in (I), showing the chains of molecules formed by the N—H···O hydrogen bonds (thin lines). Most H atoms have been omitted for clarity.

interaction between these rings. There are also no other π – π interactions evident in the structure. In contrast, a weak intramolecular π – π interaction may be present between the 2-fluoro-3-(trifluoromethyl)phenyl ring and the pyridine ring in (II). The angle between the planes of these rings is $2.94(8)^\circ$. The distance between the ring centroids is quite long at $4.0014(10)$ Å, although the perpendicular distance from the pyridine ring centroid to the plane of the other ring is $3.8258(7)$ Å. The angle between these two vectors is 17.0° , which indicates a significant degree of offset of the two parallel rings. A stronger π – π interaction in (II) appears to exist between the 1,4-DHP rings of adjacent molecules related by a centre of inversion. The distance between the ring centroids of the molecules at (*x*, *y*, *z*) and ($-x+2$, $-y$, $-z+2$) is $3.7634(9)$ Å, while the perpendicular distance from the centroid of one ring to the plane of the other is $3.6037(6)$ Å. The angle between these two vectors is 16.8° and the slippage of the centroids is 1.09 Å.

In compound (I), an intermolecular N—H···O hydrogen bond between the amine group and the carbonyl O atom of the oxocyclopentene ring of a neighbouring molecule (Table 2 and Fig. 3) links the molecules into extended chains which run parallel to the [010] direction and can be described by a graph-set motif of $C(6)$ (Bernstein *et al.*, 1995). The same $C(6)$ motif has been observed in the crystal structures of several other closely related 1,4-DHP compounds (Linden *et al.*, 1998, 2002, 2004, 2005, 2006; Şimşek *et al.*, 2000). There are no significant inter- or intramolecular C—H···*X* (*X* = O, N or halogen) interactions in the structure.

A more unusual hydrogen bond is present in the structure of (II). This time, the amine group forms an intermolecular N—H···N hydrogen bond with the pyridine ring N atom of a neighbouring molecule (Table 4 and Fig. 4). This interaction links the molecules into extended chains which run parallel to

**Figure 4**

A view, down the *b* axis, of the crystal packing in (II), showing the chains of molecules formed by the N—H···N hydrogen bonds (thin lines). The sheets formed by the additional C—H···O interactions lie parallel to the (100) plane. Most H atoms have been omitted for clarity.

the [001] direction and can be described by a graph-set motif of $C(10)$. Atom O5 of the oxocyclohexene ring now acts as an acceptor of a weak C—H···O interaction from atom C15—H of a neighbouring molecule. This interaction links the molecules into extended chains which run parallel to the [010] direction and can be described by a graph-set motif of $C(12)$. A further C—H···O interaction between C7—H and ester atom O1 of another neighbouring molecule forms a centrosymmetric $R_2^2(18)$ ring. The combination of all the hydrogen-bonding interactions in (II) leads to sheets of molecules which lie parallel to the (100) plane.

Experimental

Compounds (I) and (II) were prepared according to the method described by Şimşek *et al.* (2008) by refluxing the appropriate dicarbonyl compound, 2,3-disubstituted benzaldehyde, acetoacetate derivative and ammonium acetate in methanol for 8 h. After cooling, compound (I) was poured into ice–water. The obtained precipitate was crystallized from ethyl acetate to give diffraction quality crystals (yield 35%, m.p. 445 K). Analysis calculated for $C_{23}H_{19}ClFNO_3$: C 67.07, H 4.65, N 3.40%; found: C 66.67, H 4.67, N 3.40%. Compound (II) was obtained in a crystalline state suitable for crystallographic analysis after cooling the reaction mixture (yield 79%, m.p. 462 K). Analysis calculated for $C_{26}H_{24}F_4N_2O_3$: C 63.93, H 4.95, N 5.73%; found: C 63.76, H 4.86, N 5.86%. The structures of the compounds were elucidated by IR, 1H NMR, ^{13}C NMR and mass spectroscopy; the spectroscopic details are available in the archived CIF.

Compound (I)

Crystal data

$C_{23}H_{19}ClFNO_3$	$V = 1988.58(7)$ Å ³
$M_r = 411.86$	$Z = 4$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 10.7944(2)$ Å	$\mu = 0.23$ mm ^{−1}
$b = 13.5205(3)$ Å	$T = 160$ K
$c = 14.0573(3)$ Å	$0.30 \times 0.28 \times 0.15$ mm
$\beta = 104.2378(13)^\circ$	

Data collection

Nonius KappaCCD area-detector diffractometer	49390 measured reflections
Absorption correction: multi-scan (Blessing, 1995)	4536 independent reflections
$T_{\min} = 0.914$, $T_{\max} = 0.974$	3193 reflections with $I > 2\sigma(I)$
	$R_{\text{int}} = 0.076$

Table 1

Selected geometric parameters (Å, °) for (I).

O1—C9	1.214 (2)	C3—C9	1.480 (3)
O2—C9	1.350 (2)	C3—C4	1.533 (2)
N1—C7a	1.353 (2)	C4—C4a	1.503 (3)
N1—C2	1.395 (2)	C4a—C7a	1.354 (2)
C2—C3	1.353 (2)		
C2—N1—C7a	120.52 (16)	C3—C4—C4a	109.00 (14)
N1—C2—C3	120.74 (17)	C4—C4a—C7a	123.67 (16)
N1—C2—C8	111.90 (16)	N1—C7a—C4a	122.29 (17)
C3—C2—C8	127.37 (17)	O1—C9—O2	122.37 (17)
C2—C3—C4	123.47 (17)	O1—C9—C3	127.26 (17)
C2—C3—C9	120.55 (16)	O2—C9—C3	110.36 (15)

Table 2

Hydrogen-bond geometry (Å, °) for (I).

<i>D</i> —H··· <i>A</i>	<i>D</i> —H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> —H··· <i>A</i>
N1—H1···O5 ⁱ	0.88 (2)	1.92 (2)	2.772 (2)	163 (2)

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

Refinement

 $R[F^2 > 2\sigma(F^2)] = 0.048$ $wR(F^2) = 0.130$ $S = 1.03$

4536 reflections

268 parameters

H atoms treated by a mixture of independent and constrained refinement

 $\Delta\rho_{\max} = 0.31 \text{ e \AA}^{-3}$ $\Delta\rho_{\min} = -0.22 \text{ e \AA}^{-3}$

Compound (II)

Crystal data

 $\text{C}_{26}\text{H}_{24}\text{F}_4\text{N}_2\text{O}_3$ $M_r = 488.48$ Monoclinic, $P2_1/c$ $a = 11.3696 \text{ (2) \AA}$ $b = 9.2177 \text{ (2) \AA}$ $c = 21.9577 \text{ (3) \AA}$ $\beta = 92.5683 \text{ (11)^\circ}$ $V = 2298.89 \text{ (7) \AA}^3$ $Z = 4$ Mo $K\alpha$ radiation $\mu = 0.11 \text{ mm}^{-1}$ $T = 160 \text{ K}$ $0.25 \times 0.25 \times 0.25 \text{ mm}$

Data collection

Nonius KappaCCD area-detector diffractometer

49934 measured reflections

5242 independent reflections

3791 reflections with $I > 2\sigma(I)$ $R_{\text{int}} = 0.056$

Refinement

 $R[F^2 > 2\sigma(F^2)] = 0.049$ $wR(F^2) = 0.133$ $S = 1.03$

5242 reflections

324 parameters

H atoms treated by a mixture of independent and constrained refinement

 $\Delta\rho_{\max} = 0.29 \text{ e \AA}^{-3}$ $\Delta\rho_{\min} = -0.27 \text{ e \AA}^{-3}$

The amine H atoms were placed in the positions indicated by difference electron-density maps and their positions were allowed to refine together with individual isotropic displacement parameters. The methyl H atoms were constrained to an ideal geometry, with $\text{C—H} = 0.98 \text{ \AA}$ and $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$, but were allowed to rotate freely about their adjacent C—C bonds. All other H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms, with $\text{C—H} = 0.95$ (aromatic), 0.99 (methylene) or $1.00 \text{ \AA}$ (methine) and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$.

Table 3

Selected geometric parameters (Å, °) for (II).

O1—C10	1.209 (2)	C3—C10	1.466 (2)
O2—C10	1.360 (2)	C3—C4	1.527 (2)
N1—C8a	1.373 (2)	C4—C4a	1.517 (2)
N1—C2	1.385 (2)	C4a—C8a	1.353 (2)
C2—C3	1.353 (2)		
C2—N1—C8a	122.48 (14)	C3—C4—C4a	111.13 (12)
N1—C2—C3	120.37 (15)	C4—C4a—C8a	122.22 (15)
N1—C2—C9	112.87 (14)	N1—C8a—C4a	120.97 (15)
C3—C2—C9	126.76 (15)	O1—C10—O2	121.85 (15)
C2—C3—C4	122.23 (14)	O2—C10—C3	110.26 (14)
C2—C3—C10	121.32 (15)	O1—C10—C3	127.89 (15)

Table 4

Hydrogen-bond geometry (Å, °) for (II).

<i>D</i> —H··· <i>A</i>	<i>D</i> —H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> —H··· <i>A</i>
N1—H1···N2 ⁱ	0.90 (2)	2.11 (2)	3.0073 (19)	169.5 (19)
C7—H72···O1 ⁱⁱ	0.99	2.54	3.427 (3)	149
C15—H15···O5 ⁱⁱⁱ	0.95	2.58	3.172 (2)	120

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

For both compounds, data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97* and *PLATON* (Spek, 2009).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3400). Services for accessing these data are described at the back of the journal.

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