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3,19-(2,6-Dimethoxybenzylidene)andrographolide

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The title compound, (*E*)-3-{2-[3-(2,6-dimethoxyphenyl)-6a,10*b*-dimethyl-8-methylene-decahydro-1*H*-naphtho[2,1-*d*]-[1,3]dioxin-7-yl]ethylidene}-4-hydroxy-4,5-dihydrofuran-2(3*H*)-one, $C_{29}H_{38}O_7$, an andrographolide analogue, was semi-synthesized from andrographolide. The structure contains three fused six-membered rings adopting chair conformations and a five-membered ring adopting a twisted conformation. Intermolecular O—H···O hydrogen bonds link the molecules into chains along the *a* axis which are interlinked *via* C—H···π interactions.

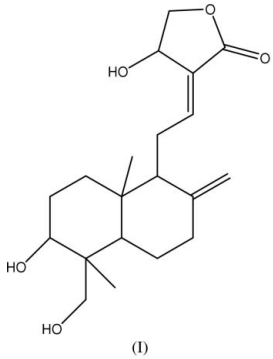
Key indicators

Single-crystal X-ray study
T = 100 K
Mean σ(C–C) = 0.002 Å
R factor = 0.043
wR factor = 0.116
Data-to-parameter ratio = 16.4

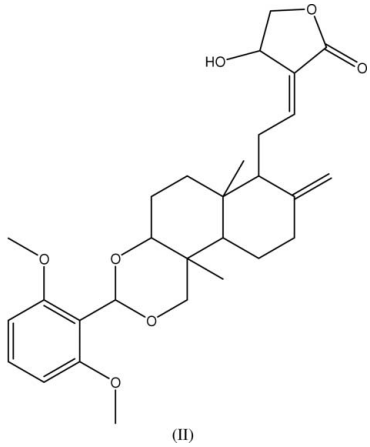
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Comment

Andrographolide, (I), is a major component of labdane-type diterpene lactones isolated from *Andrographis paniculata* Nees. Previously, we have reported the crystal structure of 3,19-(2-bromobenzyledine)andrographolide (Ng *et al.*, 2006), a lead antitumour agent of andrographolide analogues. In a subsequent study of derivatization of andrographolide, we have synthesized the title compound, (II), by reacting compound (I) with 2,6-dimethoxybenzaldehyde. These compounds were synthesized with the aim of improving the antitumour potential of the parent compound, (I). Compound (II) was tested for cytotoxic activity in breast, lung and prostate cancer cell lines and it exhibited 50% inhibitory concentrations (IC_{50}) in the submicromolar range. The present X-ray crystal structure analysis of (II) was undertaken in order to establish its molecular structure and stereochemistry.



(I)



(II)

The molecular structure of (II) is shown in Fig. 1. The bond lengths and angles have normal values (Allen *et al.*, 1987) and agree well with those found in related structures (Ng *et al.*, 2006; Spek *et al.*, 1987; Smeets *et al.*, 1987).

The dioxane ring (C5/C6/O1/C7/O2/C8) and the C4/C5/C8–C11 cyclohexane ring in the andrographolide skeleton adopt

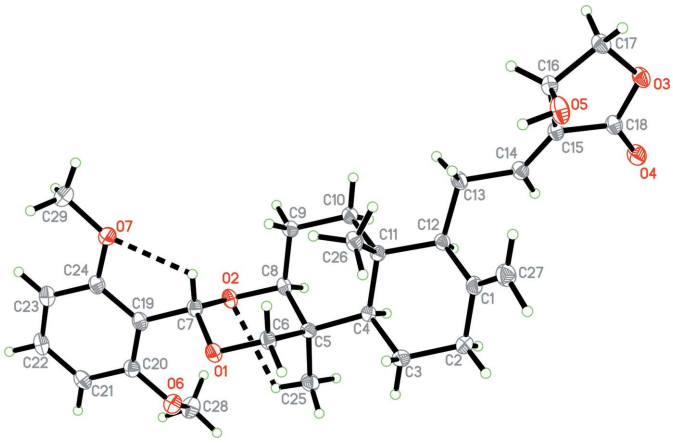


Figure 1
The molecular structure of (II), showing 50% probability displacement ellipsoids and the atomic numbering. Hydrogen bonds are shown as dashed lines.

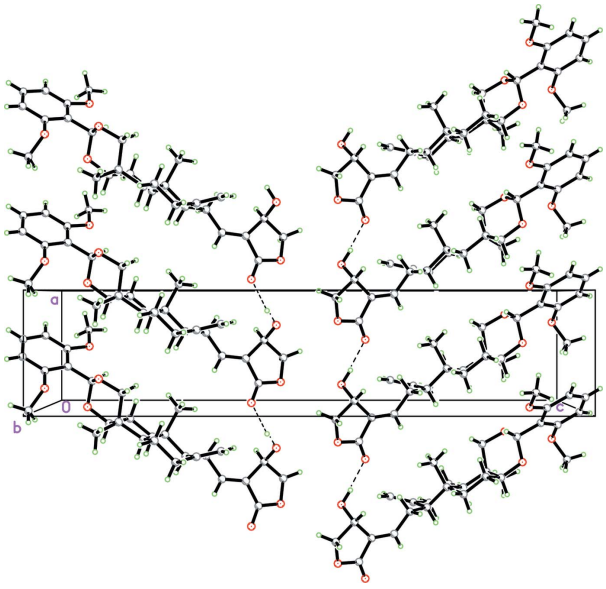


Figure 2
The crystal packing of (II), viewed down the *b* axis. Hydrogen bonds are shown as dashed lines.

chair conformations, with Cremer & Pople (1975) puckering parameters Q = 0.560 (2) Å, θ = 4.4 (2)° and φ_2 = 30 (2)° for the dioxane ring, and Q = 0.557 (2) Å, θ = 174.3 (2)° and φ_2 = 55 (2)° for the C4/C5/C8–C11 cyclohexane ring. A similar conformation is observed in related structures, *viz*. neoandrographolide monohydrate (Smeets *et al.*, 1987) and andrographolide (Spek *et al.*, 1987). The C1–C4/C11/C12 cyclohexane ring also adopts a chair conformation, with Q = 0.593 (2) Å, θ = 2.1 (2)° and φ_2 = 307 (5)°. The five-membered ring (C15–C17/O3/C18) is twisted about the C17—C16 bond, with puckering parameters Q_2 = 0.194 (2) Å and φ_2 = 238.3 (5)°.

The methoxy group at C24 is coplanar with the benzene ring, whereas that at C20 is twisted away, with the C28—O6—C20—C19 torsion angle being −114.5 (2)°.

The intramolecular C7—H7*A*···O7 and C25—H25*A*···O2 interactions (Table 1 and Fig. 1) generate *S*(5) ring motifs (Bernstein *et al.*, 1995). In the crystal structure, the molecules are linked along the *a* axis by intermolecular O5—H5*A*···O4^{i} hydrogen bonds, forming a chain (Fig. 2). In addition, the crystal packing is stabilized by a weak intermolecular C—H···π interaction (Table 1) involving the C19–C24 aromatic ring (centroid *Cg*1).

Experimental

A mixture of andrographolide (100 mg, 0.29 mmol), 2,6-dimethoxybenzaldehyde (96.4 mg, 0.58 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate in benzene–dimethyl sulfoxide (5.0 ml:0.5 ml) was refluxed for 1 h. After completion of the reaction (checked by thin-layer chromatography), the reaction mixture was cooled to room temperature and the remaining catalyst was quenched with excess triethylamine (a few drops). The reaction mixture was diluted with benzene and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The final residue was purified using column chromatography over silica gel with dichloromethane–methanol (98:2, *v*/*v*) as the eluting solvent system. After evaporation of the solvent, compound (II) (99.8 mg, 69%) was recrystallized from methanol as colourless crystals.

Crystal data

$C_{29}H_{38}O_7$
M_r = 498.59
Orthorhombic, $P2_12_12_1$
a = 6.5021 (1) Å
b = 12.9728 (2) Å
c = 29.5163 (4) Å
V = 2489.71 (6) Å^3
Z = 4
D_x = 1.330 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 100.0 (1) K
Block, colourless
0.37 × 0.26 × 0.21 mm

Data collection

Bruker SMART APEXII CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2005)
T_{min} = 0.873, T_{max} = 0.981
44842 measured reflections
5470 independent reflections
4724 reflections with $I > 2\sigma(I)$
R_{int} = 0.056
θ_{max} = 33.5°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.043
$wR(F^2)$ = 0.116
S = 1.09
5470 reflections
333 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0567P)^2 + 0.437P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.34 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

*Cg*1 is the centroid of the C19–C24 aromatic ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C7—H7*A*···O7	0.98	2.29	2.761 (2)	109
C25—H25*A*···O2	0.96	2.53	2.939 (2)	106
O5—H5*A*···O4^{i}	0.92 (4)	1.87 (4)	2.787 (2)	174 (3)
C23—H23*A*···*Cg*1^{ii}	0.93	2.82	3.679 (2)	154

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

The O-bound H atom was located in a difference map and refined isotropically. The remaining H atoms were positioned geometrically and treated as riding, with C—H distances in the range 0.93–1.03 Å. The U_{iso} values were constrained to be $1.5U_{eq}$ of the carrier atom for methyl H atoms and $1.2U_{eq}$ for the remaining H atoms. A rotating-group model was used for the methyl groups. In the absence of significant anomalous dispersion effects, Friedel pairs were merged before the final refinement.

Data collection: *APEX2* (Bruker, 2005); cell refinement: *APEX2*; data reduction: *SAINT* (Bruker, 2005); program(s) used to solve structure: *SHELXTL* (Sheldrick, 1998); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 2003).

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