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# 3,19-(2-Bromobenzylidene)andrographolide

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**Key indicators**

Single-crystal X-ray study
*T* = 297 K
Mean σ(C–C) = 0.003 Å
*R* factor = 0.049
*wR* factor = 0.109
Data-to-parameter ratio = 36.3

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



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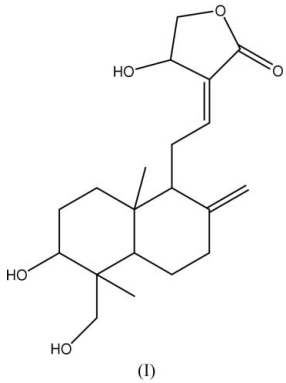
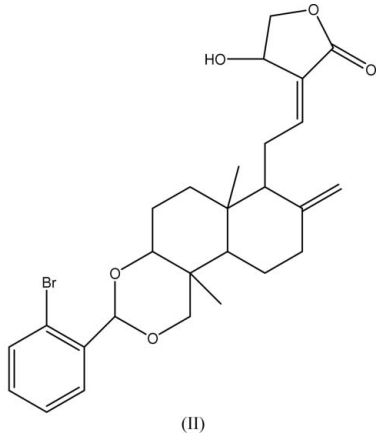
The title compound, (*E*)-3-{2-[3-(2-bromophenyl)-6a,10*b*-dimethyl-8-methyleneperhydronaphtho[2,1-*d*][1,3]dioxin-7-yl]-ethylidene}-4-hydroxy-4,5-dihydrofuran-2(3*H*)-one, $C_{27}H_{33}BrO_5$, an andrographolide derivative, was semi-synthesized using andrographolide as a starting material. The structure contains three fused six-membered rings adopting chair conformations and a five-membered ring adopting an envelope conformation. The 2-bromophenyl group is twisted away from the attached ring. O—H···O hydrogen bonds in the structure form chains along the *b* axis which are interlinked *via* C—H···O interactions.

## Comment

*Andrographis paniculata* Nees (Acanthaceae) is one of the most important medicinal plants, having been used in Chinese traditional and Indian Ayurvedic medicine for a wide range of illnesses. Extensive research on this plant extract and its constituents has revealed various pharmacological properties including anticancer and immunostimulatory activities (Kumar *et al.*, 2004, and references therein).




(I)




(II)

The active chemical constituents reponsible for the pharmacological activities of *A. paniculata* are the labdane-type diterpene lactones, among which the major component is andrographolide (I). The stereochemistry of compound (I) has previously been established (Smith *et al.*, 1982; Fujita *et al.*, 1984; Spek *et al.*, 1987). Recent studies suggested that andrographolide is an interesting pharmacophore with anticancer and immunomodulatory activities and hence has the potential to be developed as a cancer chemotherapeutic agent (Stanslas *et al.*, 2001; Rajagopal *et al.*, 2003).

With the objective of developing andrographolide analogues with increased potency and good selectivity against

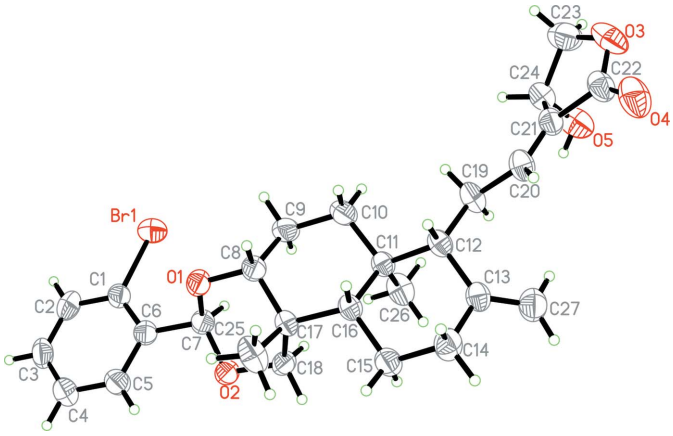



**Figure 1**
The structure of (II), showing 50% probability displacement ellipsoids and the atomic numbering.

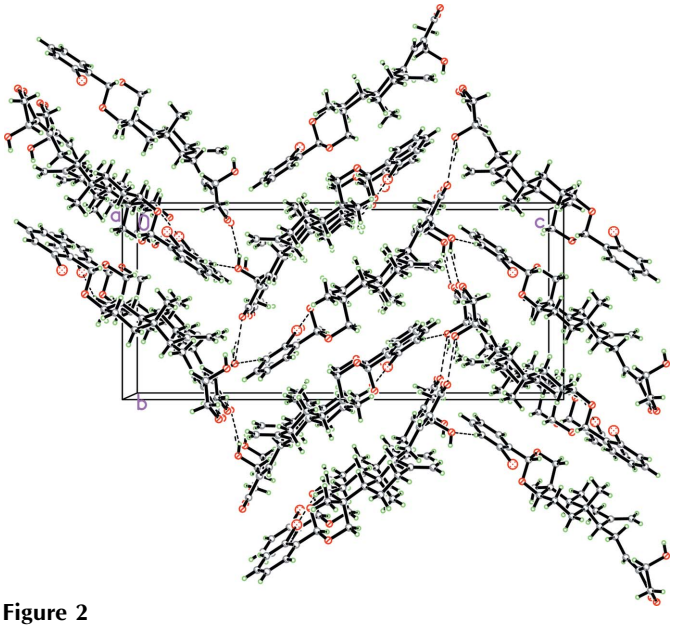



**Figure 2**
The crystal packing of (II), viewed down the *a* axis. Hydrogen bonds are shown as dashed lines.

human cancer cell lines, we subjected (I) to many semi-synthetic procedures yielding various structural analogues of this compound. Being one of the most promising anticancer andrographolide analogues, the title compound (II) exhibited potency and better selectivity in NCI-USA cancer screening when compared with the parent compound (I). We have synthesized the title compound (II) by reacting (I) with 2-bromobenzaldehyde at room temperature. The X-ray crystal structure analysis of (II) was undertaken in order to establish its molecular structure and stereochemistry.

The molecular structure of (II) is shown in Fig. 1. The bond lengths and angles have normal values (Allen *et al.*, 1987) and are comparable to those in related structures (Fujita *et al.*, 1984; Spek *et al.*, 1987; Smeets *et al.*, 1987).

The dioxane and C8–C11/C16–C17 cyclohexane rings in the andrographolide skeleton adopt chair conformations; the puckering parameters (Cremer & Pople, 1975) $Q$ = 0.566 (2) Å, $\theta$ = 175.4 (2)° and $\varphi_2$ = 318 (3)° for the dioxane ring, and $Q$ = 0.537 (2) Å, $\theta$ = 8.0 (2)°, $\varphi_2$ = 98.2 (2)° for the C8–C11/C16–C17 cyclohexane ring. A similar conformation is observed in related structures, *viz*. grapholide (Smeets *et al.*, 1987) and andrographolide (Spek *et al.*, 1987). The C11–C16 cyclohexane ring also has a chair conformation with $Q$ = 0.588 (2) Å, $\theta$ = 173.2 (2)° and $\varphi_2$ = 163.3 (2)°. The five-membered ring (C21–C22/O3/C23–C24) is in an envelope conformation, with a maximum deviation of 0.172 (3) Å for C24. The puckering parameters are $Q(2)$ = 0.275 (3) Å and $\varphi_2$ = 115.5 (6)°. The 2-bromophenyl substituent is twisted away from the dioxane ring, with torsion angles C1—C6—C7—O2 of −163.0 (2)° and C1—C6—C7—O1 of 76.1 (3)°.

Hydroxy atom O5 acts as a donor in the O5—H5*A*···O4($-x, \frac{1}{2}+y, \frac{3}{2}-z$) hydrogen bond and acceptor in the C2—H2···O5($-\frac{1}{2}-x, 1-y, -\frac{1}{2}+z$) interaction (Table 1). The molecules are linked along the *b* axis through the O—H···O intermolecular hydrogen bonds to form chains. The chains are interlinked *via* the C—H···O interactions (Fig. 2).

## Experimental

A mixture of andrographolide (500 mg, 1.43 mmol), 2-bromobenzaldehyde (4.0 g, 21.62 mmol) and a catalytic amount of $ZnCl_2$ was stirred for 4 h at room temperature. After completion of the reaction (checked by thin-layer chromatography), the reaction mixture was diluted with dichloromethane and washed with water. The organic layer was dried over $Na_2SO_4$ and then was concentrated. The final residue was purified using column chromatography over silica gel with hexane–ethyl acetate (1:1 *v*/*v*) as an eluting solvent system. After slow evaporation of the solvent, compound (II) (457 mg, 62%) formed as colourless crystals (m.p. 501.1–503.1 K).

*Crystal data*

$C_{27}H_{33}BrO_5$
$M_r$ = 517.44
Orthorhombic, $P2_12_12_1$
$a$ = 7.6735 (1) Å
$b$ = 11.7744 (2) Å
$c$ = 26.4742 (5) Å
$V$ = 2391.97 (7) Å$^3$
$Z$ = 4
$D_x$ = 1.437 Mg m$^{-3}$
Mo $K\alpha$ radiation
Cell parameters from 5896 reflections
$\theta$ = 1.5–36.2°
$\mu$ = 1.76 mm$^{-1}$
$T$ = 297 (2) K
Block, colourless
0.40 × 0.26 × 0.19 mm

*Data collection*

Bruker SMART APEX2 CCD area-detector diffractometer
$\omega$ scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2005)
$T_{min}$ = 0.417, $T_{max}$ = 0.732
36359 measured reflections
10919 independent reflections
4609 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.058
$\theta_{max}$ = 36.2°
$h = -12 \rightarrow 12$
$k = -15 \rightarrow 19$
$l = -43 \rightarrow 24$

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.109
$S$ = 0.93
10919 reflections
301 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0329P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.30 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.24 e Å$^{-3}$
Absolute structure: Flack (1983), 4719 Friedel pairs
Flack parameter: 0.011 (6)

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

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| O5—H5$A$···O4$^{i}$ | 0.82 | 2.20 | 2.909 (3) | 145 |
| C2—H2···O5$^{ii}$ | 0.93 | 2.41 | 3.318 (4) | 164 |

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

H atoms were placed in calculated positions, with an O—H distance of 0.82 Å and C—H distances in the range 0.93–0.98 Å. The $U_{iso}$ values were constrained to be $1.5U_{eq}$ of the carrier atom for hydroxyl and methyl H atoms and $1.2U_{eq}$ for the remaining H atoms.

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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## References

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans. 2*, pp. S1–S19.
Bruker (2005). *APEX2* (Version 1.27), *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Fujita, T., Fujitani, R., Takeda, Y., Takaishi, Y., Yamada, T., Kido, M. & Miura, I. (1984). *Chem. Pharm. Bull.* **32**, 2117–2125.
Kumar, R. A., Sridevi, K., Kumar, N. V., Nanduri, S. & Rajagopal, S. (2004). *J. Ethnopharmacol.* **92**, 291–295.
Rajagopal, S., Kumar, R. A., Deevi, D. S., Satyanarayana, C. & Rajagopalan, R. (2003). *J. Expt. Ther. Oncol.* **3**, 147–158.
Sheldrick, G. M. (1998). *SHELXTL*. Version 5.1. Bruker AXS Inc., Madison, Wisconsin, USA.
Smeets, W. J. J., Spek, A. L., Duisenberg, A. J. M., Labadie, R. P., De Silva, K. T. D. & Ratnayake, S. (1987). *Acta Cryst.* C**43**, 1995–1998.
Smith, A. B., Toder, B. H., Carroll P, J. & Donohue, J. J. (1982). *J. Crystallogr. Spectrosc. Res.* **12**, 309–319.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Spek, A. L., Duisenberg, A. J. M., Labadie, R. P., Ratnayake, S., Abeysekera, A. & De Silva, K. T. D. (1987). *Acta Cryst.* C**43**, 530–532.
Stanslas, J., Liew, P. S., Iftikhar, N., Lee, C. P., Saad, S., Lajis, N., Robins, R. A., Loadman, P. & Bibby, M. C. (2001). *Eur. J. Cancer*, **37** (Suppl. 6), S169.