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3-(5,7-Dimethoxy-2,2-dimethyl-2*H*-benzo[*b*]-pyran-6-yl)propionic acid: a potential inhibitor against Leishmania

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Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.002 Å
R factor = 0.033
wR factor = 0.090
Data-to-parameter ratio = 9.8

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

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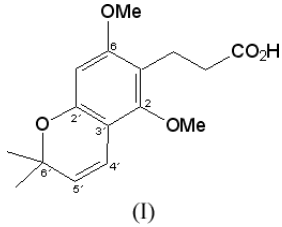
The title acid, $C_{16}H_{20}O_5$, was extracted from *Adiscanthus fusciflorus* (*Rutaceae*) and is shown to inhibit adenine phosphoribosyltransferase (APRT) enzyme activity. This compound crystallizes in the centrosymmetric space group *C*2/*c* with one molecule in the asymmetric unit. There is one strong hydrogen bond, with $O_D\cdots O_A$ = 2.6238 (12) Å and O_D—H$\cdots O_A$ = 171.1 (17)° involving the COOH group, forming a cyclic dimer about a center of symmetry. The packing of the molecules is additionally stabilized by one C—H$\cdots$O [$C_D\cdots O_A$ = 2.9820 (16) Å and C_D—H$\cdots O_A$ = 101.8 (10)°] and two C—H$\cdots\pi$ intermolecular hydrogen bonds.

Comment

The title carboxylic acid, (I), has been investigated because of its interesting inhibitory activity against adenine phosphoribosyltransferase (APRT) from *Leishmania tarentolae* which is a member of the phosphoribosyltransferase (PRTase) family. The PRTases are responsible for the salvage of purine, pyridine and pyrimidine nucleotides, as well as aromatic amino acids. Most organisms synthesize adenine nucleotides by both the *de novo* and the salvage pathways. In contrast, protozoan parasites are strict purine nucleotide auxotrophs because of the absence of a purine *de novo* biosynthetic pathway (Berens *et al.*, 1995). Therefore, these microorganisms are absolutely dependent on scavenging pre-formed purine nucleotides from the host or the media (Ullman & Carter, 1997). To look for new potential anti-leishmania drugs, we used the APRT from *L. tarentolae* as a model system to investigate the inhibitory capacity of *A. fusciflorus* extracts. The screening was performed using a spectrophotometric assay (Tuttle & Krenitsky, 1980); the IC_{50} of pure compound (I) is 147 μ*M*. In view of this interest, we have extracted the title compound, (I), and present here its crystal structure.



(I)

Compound (I) crystallizes in the centrosymmetric space group *C*2/*c* with one molecule in the asymmetric unit. The refined molecular structure, together with the atom-labeling scheme, are shown in Fig. 1 (Johnson, 1965). All the bond distances and angles are close to normal values (Allen *et al.*,

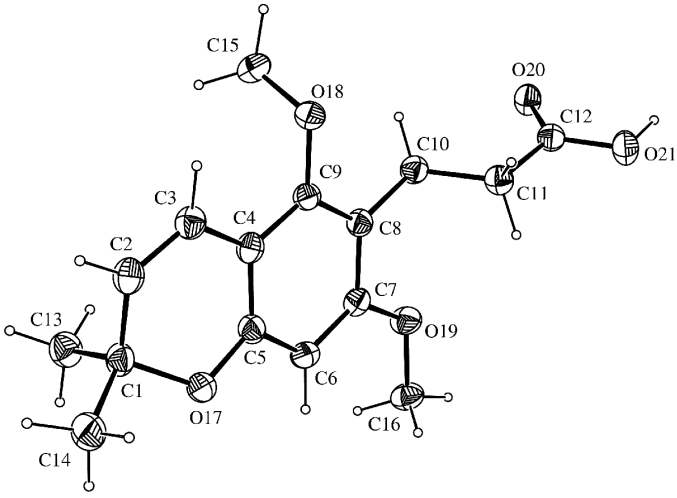


Figure 1
A view of the molecular structure of (I), showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary radii.

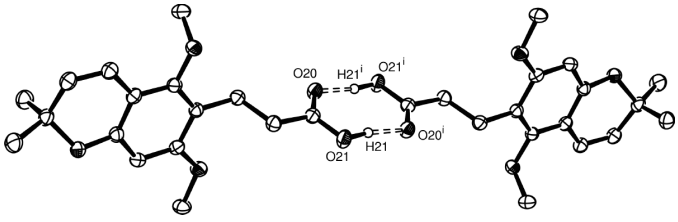


Figure 2
A view of (I), showing the dimerization due to O21—H21···O20^{i} bonding [symmetry code: (i) $\frac{1}{2}-x, \frac{1}{2}-y, 1-z$].

1983). The benzene ring C4–C9 in the central part of the molecule is very nearly planar, the maximum deviation of any of its atoms from the least-squares plane describing them being 0.0051 (8) Å, while the average deviation is 0.0030 (9) Å. Atoms (C2, C3, C16, O17, O18 and O19) around the benzene ring are coplanar [r.m.s. deviation 0.0535 (10) Å]. Thus, the structure exhibits a planar central moiety, a typical structural feature observed in anti-leishmania inhibitors (Chan-Bacab & Peña-Rodrigues, 2001).

Several packing features may be noted (Spek, 1990). There are classical intermolecular hydrogen bonds [O21—H21···O20^{i}; symmetry code: (i) $\frac{1}{2}-x, \frac{1}{2}-y, 1-z$] between the COOH groups of neighbouring molecules, forming a centrosymmetric dimer (Fig. 2). O21···O20^{i} is 2.6238 (12) Å and O21—H21···O20^{i} is 171.1 (17)°.

There is also a weak C16—H16*B*···O21^{ii} [symmetry code: (ii) $x, -y, z-\frac{1}{2}$] intermolecular hydrogen bond that is responsible for stabilization of the infinite parallel chains (Fig. 3). Furthermore, two intermolecular C—H···π interactions involve atoms C15 and C16 and the π cloud of the benzene ring. The former is between atom H15*A* and the π-ring of a molecule at $(-x, 1-y, -z)$ and the second between atom H16*A* and the molecule at $(-x, -y, -z)$. These are characterized by the distances C15···*CgBz* and C16···*CgBz* of 3.5534 (15) and 3.6568 (15) Å, respectively, and by the angles C15—H15*A*···*CgBz* and C16—H16*A*···*CgBz* of

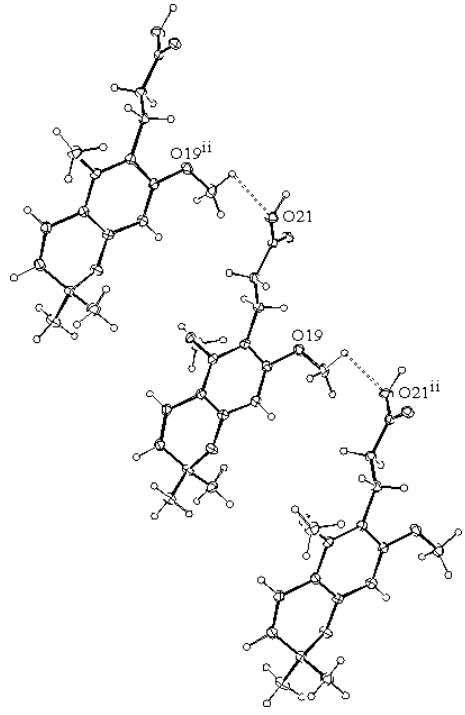


Figure 3
The crystal structure of (I). Dashed lines indicate intermolecular C16—H16*B*···O21^{ii} hydrogen bonding [symmetry code: (ii) $x, -y, z-\frac{1}{2}$].

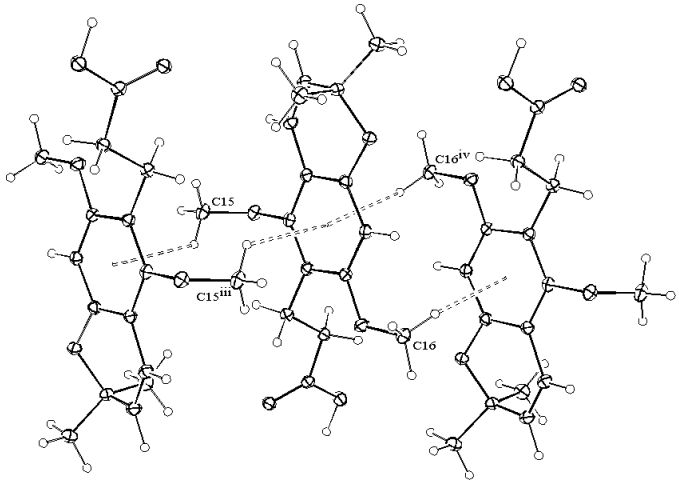


Figure 4
The C—H···π interactions in the structure of (I).

129.4 (11) and 152.2 (11)°, respectively (*CgBz* denotes the centroid of the benzene ring). These interactions link infinite parallel chains, as shown in Fig. 4. All geometrical details of the intermolecular contacts were interpreted as hydrogen bonds on geometrical grounds (Ellena *et al.*, 2001); Table 2 reports the relevant geometrical parameters.

Experimental

The roots and leaves of *A. fusciflorus* were collected in Manaus-AM/Brazil in December 2000. An authenticated specimen was deposited in the herbarium of the Instituto de Pesquisas da Amazonia, INPA/Brazil, reference code 189859. The powdered parts of the dihydrocinnamic acid title compound, isolated by extraction (roots 2.380 kg

and leaves 1.040 kg), were then extracted successively with hexane (10 l) and methanol (8.5 l). The hexane extract of the root (5.0 g) was chromatographed on an silica gel column ($\Phi \times h = 28 \times 2$ cm) using a hexane/EtOAc gradient to fractionate the extract. Nine fractions were collected. Fraction 5 (hexane–ethyl acetate 7:3) was chromatographed on an silica gel column ($\Phi \times h = 50 \times 1.5$ cm) using a gradient system of hexane, ethyl acetate and methylene chloride. 42 fractions were collected and, based on normal phase thin-layer chromatography (TLC), seven fractions were pooled. Fraction 3 (hexane/ethyl acetate/methylene chloride 7:2:1) produced an amorphous white solid (25 mg) that was washed successively with hexane and crystallized by vapor diffusion at room temperature from hexane/methylene chloride (1:1). The purity of the compound was checked by TLC (silica gel, Merck PF 254, 0.25 mm thickness).

Crystal data

$C_{16}H_{20}O_5$	$D_x = 1.278$ Mg m^{-3}
$M_r = 292.32$	Mo $K\alpha$ radiation
Monoclinic, $C2/c$	Cell parameters from 3662 reflections
$a = 23.3022$ (3) Å	$\theta = 1.0$–$27.5°$
$b = 10.2248$ (2) Å	$\mu = 0.10$ mm^{-1}
$c = 15.0785$ (3) Å	$T = 120$ (2) K
$\beta = 122.273$ (1)°	Prism, colorless
$V = 3037.60$ (9) Å^3	0.16 × 0.14 × 0.10 mm
$Z = 8$	

Data collection

Nonius KappaCCD diffractometer	$R_{int} = 0.016$
φ and ω scans	$\theta_{max} = 25°$
5170 measured reflections	$h = -27 \rightarrow 27$
2666 independent reflections	$k = -12 \rightarrow 12$
2207 reflections with $I > 2\sigma(I)$	$l = -17 \rightarrow 17$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0472P)^2 + 0.8048P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.033$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.090$	$\Delta\rho_{max} = 0.19$ e Å^{-3}
$S = 1.05$	$\Delta\rho_{min} = -0.16$ e Å^{-3}
2666 reflections	Extinction correction: *SHELXL*97
271 parameters	Extinction coefficient: 0.0043 (7)
H atoms treated by a mixture of independent and constrained refinement	

Table 1
Selected geometric parameters (Å, °).

O20—C12	1.2252 (15)	C12—O21	1.3188 (15)
O20—C12—O21	122.90 (11)	O21—C12—C11	113.66 (11)
O20—C12—C11	123.42 (11)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O21—H21···O20^{i}	1.04 (2)	1.59 (2)	2.6238 (12)	171.1 (17)
C16—H16B···O21^{ii}	1.011 (17)	2.607 (15)	2.9820 (16)	101.8 (10)
C15—H15A···$CgBz^{iii}$	1.024 (16)	2.814 (16)	3.5534 (15)	129.4 (11)
C16—H16A···$CgBz^{iv}$	0.985 (15)	2.756 (15)	3.6568 (15)	152.2 (11)

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

Atoms H15*A*, H16*A*, H16*B* and H21 were found in a Fourier synthesis and were freely refined. The other H atoms were placed at calculated positions.

Data collection: *COLLECT* (Nonius, 1997–2002); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *HKL SCALEPACK* and *DENZO* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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