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Redetermination and comparative structural study of isopimpinellin: a new inhibitor against the Leishmania APRT enzyme

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Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.002 Å
R factor = 0.044
wR factor = 0.124
Data-to-parameter ratio = 12.4

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

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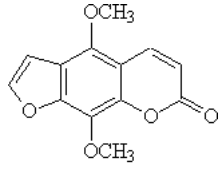
The title compound (alternative name 5,8-dimethoxypsoralen), $C_{13}H_{10}O_5$, is a natural product extracted from *Adiscanthus fusciflorus* (*Rutaceae*). Our biochemical tests show that this compound has inhibitory activity against the enzyme adenine phosphoribosyltransferase (APRT) from Leishmania, a tropical parasite causing endemic disease in poor countries. It crystallizes in the centrosymmetric space group $P2_1/c$, with one molecule in the asymmetric unit, and has at least two C—H···O intermolecular interactions, leading to the formation of centrosymmetric dimers.

Comment

Leishmaniasis is a disease caused by a protozoal parasite of the order Kinetoplastid. According to the World Heath Organization reports (WHO, 1998), 88 countries are affected, with 12 million infected people and approximately 350 million people at risk. The need for new drugs for the treatment of leishmaniasis infections comes from a lack of safe drugs and the serious secondary effects observed in available chemotherapy (McGreevy & Marsden, 1986). Looking for new bioactive substances, potentially useful against leishmaniasis, we used the PRTase adenine phosphoribosyltransferase (APRT) from *L. tarentolae* as a model system to screen the inhibitory capacity of several small molecule compounds from Brazilian plants. The screening was performed using the APRT inhibitory assay, either in the presence of extracts or with the purified compound, and was monitored spectrophotometrically (Tuttle & Krenitsky, 1980). The title compound, (I), was isolated from *A. fusciflorus* extracts and has been structurally investigated because of its inhibitory activity against APRT. A comparative study between (I) and another inhibitor , skimmianine (II) (Napolitano *et al.*, 2003), against the APRT enzyme will be performed.



(I)

Enzymatic tests of compounds (I) and (II) at 50 µg/ml show inhibition activities of 50% and 68%, respectively. Further investigations by molecular docking and dynamic simulations will be performed to study the interactions between compounds (I) and (II) and the APRT active site. The new

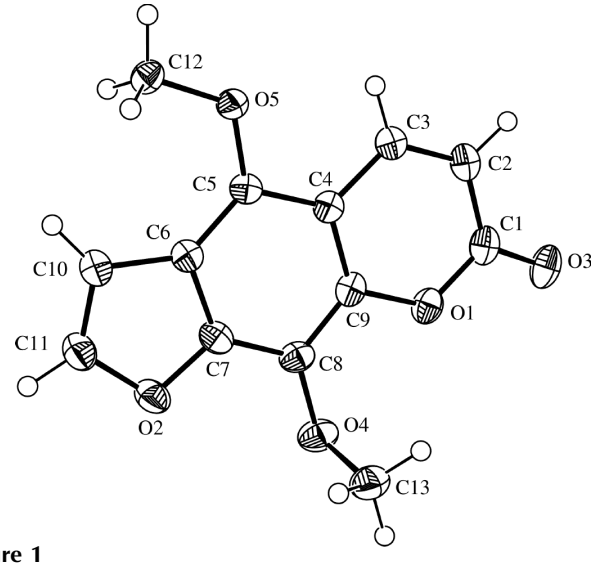


Figure 1
A view of the molecular structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary radii.

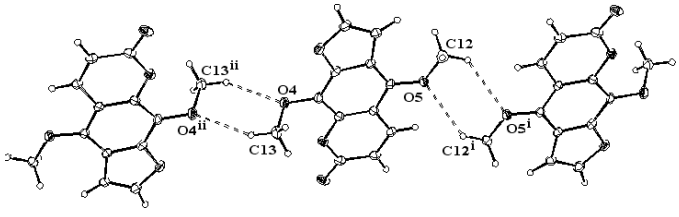


Figure 2
A view of (I), showing dimerization, viewed along the [111] direction. Dashed lines indicate intermolecular C—H···O hydrogen bonding.

information obtained will then be used to improve the inhibitory activity of these molecules. In light of this interest, a comparative structural characterization of the two compounds will give us important information with respect to the interaction modes of compounds (I) and (II) with APRT, and allow the investigation of possible inhibition of those compounds with other phosphoribosyltransferase (PRTases).

All bond lengths and angles of (I) are close to normal values (Allen *et al.*, 1983). The crystallographic structure of (I), measured at room temperature, has been previously published (Gopalakrishna *et al.*, 1977). With the aim of obtaining more accurate and comparable structural data of inhibitors (I) and (II), and in order to use this information in molecular docking and dynamic simulations, we determined the structure at 120 K. An *ORTEP* view (Farrugia, 1997) of (I), together with the atom-labelling scheme, is shown in Fig. 1.

Five significant intermolecular C—H···O contacts are found in the packing of compound (I), *viz*. C12—H12*B*···O5^{i}, C13—H13*B*···O4^{ii}, C12—H12*A*···O3^{iii}, C12—H12*C*···O3^{iv} and C11—H11···O2^{v} (symmetry codes as in Table 1). The first two interactions link neighbouring molecules in a centrosymmetric dimeric form, giving rise to tan infinite chain of these dimers along the [111] direction, as seen in Fig. 2. The third and fourth interactions form an infinite chain along the *c* axis. The last interaction links two dimeric chains along the *b* axis. All structural details of the intermolecular contacts for compound (I) were interpreted as hydrogen bonds on geometrical grounds (Ellena *et al.*, 2001).

The molecular structures of (I) and (II) present small differences in overall planarity, except for carbon C13 in both compounds. The maximum deviation of their non-H atoms from the mean least-square plane through the planar part of the molecules are 0.162 (7) Å and 0.061 (1) Å, while the average deviations are 0.0597 (9) Å and 0.031 (1) Å for (I) and (II), respectively. The C13 methoxy group of (I) has the same orientation as the C5 methoxy group of (II), both being toward the respective C—H···O interaction, as described above. The dihedral angles between the plane formed by these methoxyl groups and the plane formed by the three rings of (I) and (II) are 1.2 (2)° and 2.3 (1)°, respectively. The torsion angles C4—C3—O2—C12 for (II) and C4—C5—O5—C12 for (I) are 0.1 (2)° and 0.2 (2)°, respectively. The orientation of the C8 methoxy group of (I) toward N^{iii} allows this group to be positioned in the same ring plane. In (II), a carboxyl (instead of a methoxy) group is noted at the corresponding position.

The dihedral angles between the planes formed by the C9 methoxy group and the three rings of (I), and between the C8 methoxy group and the three rings of (I) are 89.09 (7)° and 77.95 (9)°, respectively. The torsion angles C5—C9—O3—C13 for (II) and C7—C8—O4—C13 for (I) are 93.4 (2)° and 76.8 (2)°, respectively. In both molecules, this functional group is attached to the benzene ring and in molecule (II) its orientation is driven by the intermolecular C—H···O interaction, as described above. These differences between compounds (I) and (II) seem to be consistent with the observed inhibitory activity differences against the Leishmania APRT enzyme.

Experimental

The roots and leaves of *A. fusciflorus* were collected from the Manaus region of the Brazilian Amazon forest in December 2000. An authenticated specimen was deposited in the herbarium of the Instituto de Pesquisas da Amazonia–INPA (code 189859). The powdered parts (roots 2.380 kg and leaves 1.040 kg) were extracted successively with hexane (10 l) and methanol (8.5 l). The hexane extracte of the leaves (7.8 g), when chromatographed using a silica gel column with a hexane and ethyl acetate gradient followed by methanol, gave 33 fractions. Fractions 29 and 33 were chromatographed on a Sephadex LH-20 column using methanol as the mobile phase. Thirteen fractions were collected and fractions 6 and 7 resulted in 204.2 mg of compound (I), which crystallized by vapour diffusion from dichloromethane/methanol (1:1) as solvent, yielding light yellow prismatic needles.

Crystal data

$C_{13}H_{10}O_5$
M_r = 246.21
Monoclinic, $P2_1/c$
a = 16.9357 (5) Å
b = 4.3669 (1) Å
c = 16.2558 (4) Å
β = 117.218 (1)°
V = 1069.10 (5) Å^3
Z = 4
D_x = 1.53 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2772 reflections
θ = 1.0–27.5°
μ = 0.12 mm^{-1}
T = 120 (2) K
Prism, light yellow
0.28 × 0.16 × 0.05 mm

Data collection

Nonius KappaCCD diffractometer	$R_{int} = 0.023$
φ and ω scans	$\theta_{max} = 27.5^\circ$
Absorption correction: none	$h = -21 \rightarrow 22$
4114 measured reflections	$k = -4 \rightarrow 5$
2450 independent reflections	$l = -21 \rightarrow 20$
1841 reflections with I $>2\sigma(I)$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0713P)^2$
$R[F^2 > 2\sigma(F^2)] = 0.044$	$+ 0.1752P]$
$wR(F^2) = 0.124$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.04$	$(\Delta/\sigma)_{max} < 0.001$
2450 reflections	$\Delta\rho_{max} = 0.23$ e Å^{-3}
197 parameters	$\Delta\rho_{min} = -0.3$ e Å^{-3}
All H-atom parameters refined	

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

D—H···A	D—H	H···A	D···A	D—H···A
C12—H12B···O5^{i}	1.01 (2)	2.64 (2)	3.420 (1)	134.2 (14)
C13—H13B···O4^{ii}	0.98 (2)	2.58 (2)	3.455 (2)	149.4 (16)
C12—H12A···O3^{iii}	1.01 (2)	2.41 (2)	3.264 (1)	141.3 (16)
C12—H12C···O3^{iv}	1.00 (2)	2.67 (2)	3.043 (1)	102.0 (13)
C11—H11···O2^{v}	0.96 (1)	2.45 (1)	3.360 (1)	156.7 (13)

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

All of the H atoms were found in a Fourier synthesis and were subsequently refined freely.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *HKL DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; 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) and *PLATON* (Spek, 2002); software used to prepare material for publication: *WinGX* publication routines (Farrugia, 1999).

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