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Desmosdumotin C, a novel cytotoxic principle from *Desmos dumosus*

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Abstract—The structure of desmosdumotin C (**1**), a novel compound isolated from the roots of *Desmos dumosus*, has been established from spectral data and X-ray crystallographic analysis. Significant and selective in vitro cytotoxicity of **1** was found against bone (HOS), breast (MCF), and ovarian (IA9) cancer cell lines. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Desmos dumosus (Roxb.) Saff. (Annonaceae) is a shrub growing in the southern parts of China. The leaves and roots of this species have been used as antimalarial, insecticidal, antirheumatic, antispasmodic and analgesic agents in Chinese folk medicine.[1] Many other plants in this genus have also been used as folk remedies in China and other Asian countries.

2. Results and discussion

Desmosdumotins A and B were previously isolated from the root bark of *D. dumosus*. The novelty of these structures[2,3] prompted our continuing search for additional new cytotoxic compounds from this same plant. We report herein on the isolation and structural characterization of the novel cytotoxic principle desmosdumotin C.[4–6]

Desmosdumotin C, yellow needle crystals, has the molecular formula $C_{19}H_{20}O_4$ based on the appearance of a molecular ion peak at m/z 312 and elemental analysis data. Its IR spectrum showed the presence of conjugated carbonyl groups (1670 and 1630 cm^{-1}) and aromatic rings (1580 and 1530 cm^{-1}). The ^1H NMR spectrum showed signals for a hydrogen-bonded hydroxy group (19.16 ppm, s, 1H), a methoxy group (3.95 ppm, s, 3H), an olefinic methyl group (2.00 ppm, s, 3H), two geminal methyl groups (1.38 ppm, s, 6H), an unsubstituted aromatic ring (7.39–7.66 ppm, m, 5H) and two *trans*-oriented olefinic protons (8.32 ppm, d, $J=14.7$ Hz; 7.93 ppm, d, $J=14.7$ Hz). In the ^{13}C NMR spectrum, 19 carbon signals were observed including 8 quaternary, 7 methine and 4 methyl carbons. From the foregoing results, the compound was identified as 2-[(1′-hydroxy-2′-ene-3′-phenyl) propenylene]-5-methoxy-4,6,6-trimethyl-1,3-cyclohexene(4,5)-diketone (**1**) and given the trivial name desmosdumotin C (Fig. 1). In addition, the chemical structure was confirmed by the X-ray crystallographic structure analysis as seen in Fig. 2.

Desmosdumotin C was evaluated in vitro against a panel of six cancer cell lines; the results are shown in Table 1. It showed significant (ED_{50}<4.0 μg/mL) and selective in vitro cytotoxicity against HOS bone cancer,

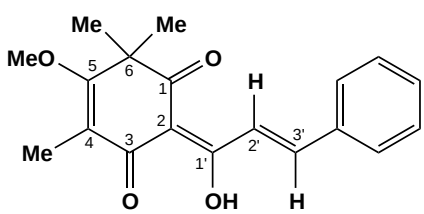

Figure 1. Desmosdumotin C (**1**)

Keywords: Desmosdumotin C; *Desmos dumosus*; cytotoxicity; antitumor.

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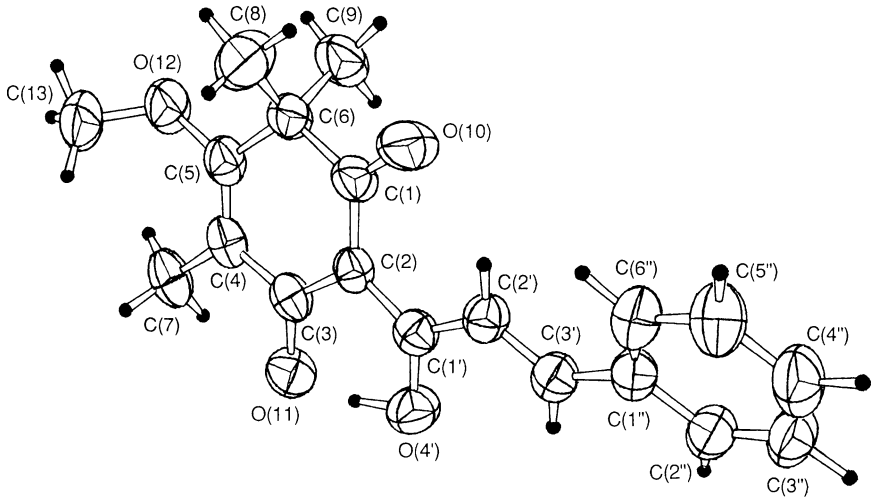

Figure 2. Solid state conformation of desmosdumotin C (**1**).

Table 1. Cytotoxic activity of desmosdumotin C (**1**)

Cancer Cell Line; ED_{50} (μg/mL)					
MCF	HOS	1A9	HCT-8	KB	KB-VIN
3.8	2.5	4.0	5.0	6.5	5.6

Values are the mean calculated from two independent experiments.

MCF-7 breast cancer, and 1A9 ovarian cancer cell lines. Moderate cytotoxicity was found against HCT-8 ileocecal cancer cells. In addition, compound **1** was more active against vincristine-resistant KB cells (ED_{50} 5.6 μg/mL) than against the parent KB epidermoid nasopharyngeal carcinoma cell line (ED_{50} 6.5 μg/mL).

Desmosdumotin C thus represents a promising new lead structure for further new analog development as potential antitumor agents. Additional structural modification and biological evaluation studies are in progress.

3. X-Ray crystal structure analysis of desmosdumotin C (1)

An Enraf-Nonius CAD-4 diffractometer (Cu Kα radiation, graphite monochromator) was used for all measurements. One octant of intensity data ($\theta_{max}=75°$, 3342 non-equivalent reflections) yielded 2031 reflections with $I>2.0\sigma(I)$ for use in the structure analysis and refinement. The data were corrected for the usual Lorentz and polarization effects; an empirical absorption correction [T_{max}:T_{min} (rel.)=1.00:0.90, derived from ϕ-scans] was also applied. The crystal structures were solved by direct methods. Full-matrix least-squares refinement of atomic positional and thermal parameters (anisotropic C, O; isotropic H) converged at $R=0.042$ ($R_w=0.054$). No unusual features were present in the final difference Fourier synthesis [$\Delta\rho$ (e/Å^3)=0.15 (max), –0.14 (min)]. Crystallographic calculations were performed by use of the Enraf–Nonius Structure Determination Package (SDP 5.0). For all structure-factor calculations, neutral atom scattering factors and their anomalous dispersion corrections were taken from the lierature.[7]

Crystal data: $C_{19}H_{20}O_4$, $M=312.37$, orthorhombic, space group *Pbca* (D_{2h}^{15})-No.61, $a=7.726(1)$, $b=36.615(5)$, $c=11.492(1)$ Å, [from diffractometer setting angles for 25 reflections ($36°<\theta<40°$) at 296 K], $V=3251(1)$ Å^3, $Z=8$, $D_{calcd}=1.276$ g cm^{-3}, absorption coefficient μ(Cu-Kα radiation, $\lambda=1.5418$ Åz0=6.9 cm^{-1}, crystal dimensions: 0.06×0.20×0.60 mm.

Copies of these data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-3360333 or e-mail: deposit@ccdc.cam.ac.uk).

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4. **Plant material.** The roots of *D. dumosus* were collected from Guangxi Zhuang Autonomous Region and identified by Professor Ding Fang.

5. **Extraction and isolation**. Dried and powdered roots of *D. dumosus* (5 Kg) were extracted with 95% EtOH (30 L) five times at room temperature. The combined percolate was concentrated under reduced pressure, and was then extracted with petroleum ether, $CHCl_3$, EtOAc and MeOH. The petroleum ether extract was concentrated under reduced pressure to give a residue, which was chromatographed on a silica gel (10–40 μ) column and eluted with a petroleum ether:EtOAc gradient (20:1–5:1). Desmosdumotin C (**1**) (900 mg) was isolated from the petroleum ether (10:1) eluate.
6. **Desmosdumotin C** (**1**): yellow needle crystals ($CHCl_3$–MeOH), mp: 93–94; UV λ_{max} (MeOH) nm (ε): 372 (2375), 233 (1362); IR (KBr) cm^{-1}: 1670, 1630, 1580, 1530, 1430, 1370, 1250, 1150, 1120, 980, 950; ^1H NMR ($CDCl_3$, TMS) δ (ppm): 19.16 (1H, s, OH), 8.32 (1H, d, $J=14.7$ Hz), 7.93 (1H, d, $J=14.7$ Hz), 7.66 (2H, m, Ar-2″, 6″-H), 7.39 (3H, m, Ar-3″, 4″, 5″-H), 3.95 (3H, s, OCH_3), 2.00 (3H, s, Ar-CH_3), 1.38 (6H, s, $CH_3\times2$). ^{13}C NMR ($CDCl_3$, TMS) δ (ppm): 197.99 (C-1), 192.34 (C-3), 187.13 (C-1′), 175.55 (C-5), 144.78 (C-2′, 3′), 135.17 (C-1″), 130.52 (C-3″, C-5″), 128.33 (C-4″), 123.19 (C-2″, 6″), 113.54 (C-2), 106.06 (C-4), 62.08 (OCH_3), 50.36 (C-6), 24.32 ($CH_3\times2$), 9.74 (Ar-CH_3); EI-MS m/z (%): 312 (M^+, 100), 297 (M^+–Me, 40), 269 (6), 235 (68), 193 (22), 165 (14), 131 (47), 103 (13), 77 (8). EA (theory: H, 6.45; C, 73.06%. Found: H, 6.45; C, 73.04%).
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