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# DEHYDROODORIN, A CYTOTOXIC DIAMIDE FROM THE LEAVES OF *AGLAIA FORMOSANA*

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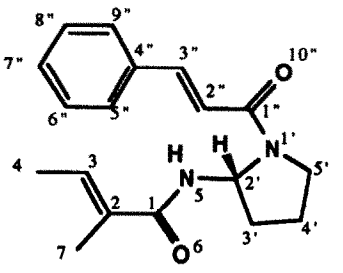
**Key Word Index**—*Aglaia formosana*; Meliaceae; leaves; cytotoxicity; dehydroodorin; P-388 cells.

**Abstract**—Bioactivity guided fractionation of a chloroform extract of the leaves of *Aglaia formosana* afforded a new cytotoxic diamide, dehydroodorin.

## INTRODUCTION

As part of a continuing search for tumour inhibitors from natural sources, *Aglaia formosana* (Hayata) Hayata was selected for study when a chloroform extract of the leaves was found to display significant cytotoxicity in A-549 (human lung adenocarcinoma), HT-29 (human colon adenocarcinoma), KB (human epidermoid carcinoma) and P-388 (mouse lymphocytic leukaemia) cell culture systems when assessed using standard protocols [1, 2].



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## RESULTS AND DISCUSSION

Bioactivity guided chromatographic fractionation led to the isolation and characterization of a new cytotoxic diamide, **1**. Compound **1** was obtained as needles, mp 167–168°, and exhibited a molecular formula of $C_{18}H_{22}O_2N_2$ as determined by high resolution mass spectrometry. Presence of a cinnamoyl moiety was indicated by the appearance of mass peaks at *m/z* 131 (PHCH=CHCO) and 103 (PHCH=CH), by IR bands (KBr) at 1660, 1620, 1520, 1415 and 990 $cm^{-1}$ and substantiated by the presence in the $^1H$ NMR spectrum ($CDCl_3$) of a characteristic lowfield signal at $\delta$7.69 (1H, *d*, $J=15.4$ Hz, H-3″), 6.94 (1H, *d*, $J=15.4$ Hz, H-2″), and 7.20–7.50 (5H, *m*, aromatic protons). $^1H$–$^1H$ COSY experiment yielded the following assignments: $\delta$1.72 (3H, *d*, $J=7.0$ Hz, H-4), 1.82 (3H, *d*, $J=1.2$ Hz, H-7), 1.70–1.98 (2H, *m*, H-4′), 1.90–2.25 (2H, *m*, H-3′), 3.20–3.56 (2H, *m*, H-5′), 6.08–6.18 (1H, *m*, H-2′), 6.48–6.60 (1H, *m*, H-3), 7.48 (1H, *m*, NHCO). The presence of this amide amino group was also reflected by an IR band at 3270 $cm^{-1}$. The foregoing evidence led to the conclusion that **1** represented the structure of the cytotoxic diamide and this was supported by its $^{13}C$ NMR spectrum ($CDCl_3$): $\delta$170.1 (*s*, C-1), 167.3 (*s*, C-1″), 143.8 (*d*, C-3″), 136.2 (*s*, C-2), 132.8 (*d*, C-3), 131.0 (*d*, C-7″), 130.1 (*d*, C-6″, 8″), 129.4 (*d*, C-5″, 9″), 119.5 (*d*, C-2″), 64.1 (*d*, C-2′), 46.8 (*t*, C-5′), 34.8 (*t*, C-3′), 21.9 (*t*, C-4′), 14.3 (*q*, C-7), 12.5 (*q*, C-4). The assignment of the $^{13}C$ NMR chemical shift of **1** was achieved by the application of $^1H$–$^{13}C$ hetero-nuclear shift correlated 2D experiments [3]. The relative configuration of **1** was determined by X-ray diffraction analysis (Fig. 1). Compound **1** exhibited cytotoxicity against P-388 lymphocytic leukaemia system in cell culture with $ED_{50}$ of 3.86 $\mu g\,ml^{-1}$.

## EXPERIMENTAL

Mps: uncorr. $^1H$ NMR (200 MHz): $CDCl_3$. MS: 70 eV direct inlet. UV: MeOH. IR: KBr. Chromatographic sepns were carried out on silica gel G. TLC spots were detected under UV (254 and 365 nm) and heating the plates to 100° after spraying with 60% $H_2SO_4$.

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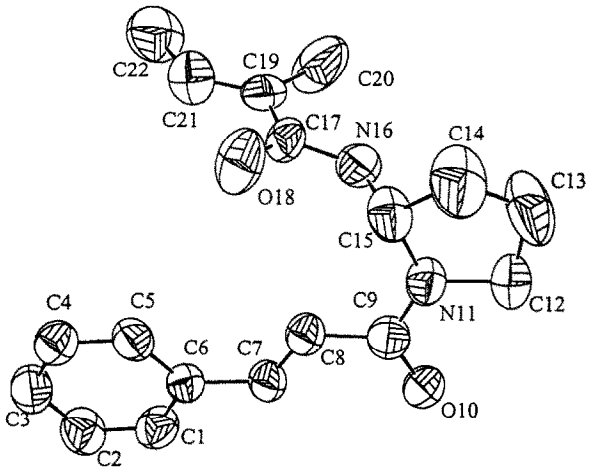


Fig. 1. Molecular structure of dehydroodorin (**1**).

*Plant material. Aglaia formosana* was collected in Man-Chou, Ping-Tong County in January 1991. Voucher specimens are kept in the Graduate Institute of Natural Products, Kaohsiung Medical College, Kaohsiung, Taiwan.

*Extraction and fractionation.* Air-dried, milled leaves (10.5 kg) were extracted repeatedly with MeOH. After removal of solvent *in vacuo*, the MeOH-soluble residue was partitioned between $H_2O$ and $CHCl_3$. The dried $CHCl_3$ extract (650 g) was found to exhibit cytotoxicity in A-549, HT-29, KB and P-388 cell culture systems when assessed using standard protocols [1, 2]. CC of the $CHCl_3$ extract was undertaken using $CHCl_3$ and $CHCl_3$–MeOH mixt. of increasing polarity. A total of 212 frs (200 ml) was collected. Elution with $CHCl_3$ afforded frs containing **1**. Further purification by CC with *n*-hexane–EtOAc (1:1) as eluent solvent afforded **1**.

*Dehydroodorin* (**1**). Obtained from MeOH as needles (120 mg), mp 167–168°, $[\alpha]_D^{18}$ +42.5° ($CHCl_3$; *c* 0.01), UV $\lambda_{max}$ nm (log $\varepsilon$): 282 (4.82), IR $\nu_{max}$ $cm^{-1}$: 3270, 1660, 1620, 1520, 1415, 990 $cm^{-1}$; MS *m/z* (rel. int.): 298 $[M]^+$, 281 (0.4), 265 (0.2), 256 (0.3), 243 (0.1), 236 (0.2), 229 (0.6), 215 (15), 200 (4), 199 (21), 167 (35), 151 (6), 131 (100), 103 (59), 85 (52), 83 (44), 77 (28), 70 (15).

*X-Ray analysis of* **1**. The derived molecular structure is depicted in Fig. 1.

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