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A Novel Cyclooxygenase-Inhibitory Stilbenolignan from the Seeds of *Aiphanes aculeata*

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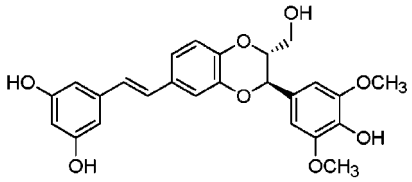
ABSTRACT



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Aiphanol (1), a novel stilbenolignan, along with isorhapontigenin (2), piceatannol (3), and luteolin, were isolated by bioassay-guided fractionation from the seeds of *Aiphanes aculeata* Willd. (Arecaceae). The structure of compound 1 was elucidated by spectroscopic methods. Compound 1 is based on an unprecedented stilbenolignan skeleton in which a stilbene moiety is linked with a phenylpropane unit through a dioxane bridge. Compounds 1 and 2 exhibited significant inhibitory activities against cyclooxygenases-1 and -2.

Stilbenoids have been found in a number of plant species and are of interest from a pharmacological point of view.[1−3] Recently, Pezzuto and colleagues established the cancer chemopreventive potential of *trans*-resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) in various assays reflective of the three major stages of carcinogenesis.[4,5] In our search for naturally occurring cancer chemopreventive agents, the seeds of *Aiphanes aculeata* Willd. (Arecaceae),[6] collected in Peru, were investigated. No previous biological and phytochemical investigations on this plant have been reported. The bioassay-guided chromatographic separation of an EtOAc-soluble extract of *A. aculeata* using the in vitro cyclooxygenase-1 (COX-1) inhibitory assay resulted in the isolation of a novel stilbenolignan, aiphanol (**1**), as well as the known stilbenes, isorhapontigenin (**2**)[7] and piceatannol (**3**),[8] and the flavone, luteolin.[9] Compound **1** represents a novel carbon skeleton having a stilbene−phenylpropane unit with a dioxane moiety. This communication deals with the isolation and structural characterization of **1** and the biological evaluation of the four compounds isolated.

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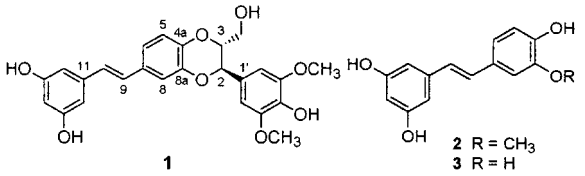
The dried seeds of *A. aculeata*[10] (5.8 kg) were ground and extracted with MeOH by maceration. After filtration and concentration, the resultant extract was partitioned with hexane and EtOAc, respectively, to afford hexane-soluble (48.0 g) and EtOAc-soluble (51.0 g) residues. Bioassay-guided fractionation of the EtOAc-soluble residue using the cyclooxygenase-1 (COX-1) inhibitory assay, applying successive Si gel and Sephadex LH-20 column chromatography and HPLC steps, resulted in the isolation of aiphanol[11] (**1**, 6.0 mg, 0.00008% w/w), along with three known constituents, isorhapontigenin[7] (**2**, 8.0 mg, 0.00014% w/w), piceatannol[8] (**3**, 250 mg, 0.0043% w/w), and luteolin[9] (9.0 mg, 0.00015% w/w).



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Compound **1** was obtained as an amorphous brown powder and was shown to possess a molecular formula of $C_{25}H_{24}O_8$ by HRMS. The ^{1}H NMR spectrum of **1** showed protons of an AMX system at δ_H 6.90 (1H, d, J = 8.3 Hz, H-5), δ_H 7.08 (1H, dd, J = 1.9 and 8.4 Hz, H-6), and δ_H 7.13 (1H, d, J = 1.9 Hz, H-8), protons of an AX_2 system at δ_H 6.56 (2H, d, J = 2.0 Hz, H-12) and δ_H 6.28 (1H, brt, J = 1.9 Hz, H-14), and signals of a trans double bond at δ_H 6.94 (1H, d, J = 16.4 Hz, H-9) and δ_H 7.02 (1H, d, J = 16.3 Hz, H-10). These signals were suggestive of the presence of a stilbene moiety,[7,8] which was substantiated by the HMQC NMR experiment. Additionally, signals at δ_H 4.97 (1H, d, J = 8.1 Hz, H-2), δ_H 4.14 (1H, multiplet, H-3), δ_H 3.53 (1H, dd, J = 4.1, 12.3 Hz, CH_2OH), δ_H 3.74 (1H, dd, J = 2.3, 12.4 Hz, CH_2OH), δ_H 6.84 (2H, singlet, H-2′), and δ_H 3.86 (3H, singlet, OCH_3) were observed. Careful analysis of the COSY and HMBC NMR data indicated that compound **1** also has a phenylpropane unit.[12] The deshielded doublet at δ_H 4.97 (H-2), typical of a benzylic methine substituted by an oxygen, and the multiplet at δ_H 4.14 (H-3), which were coupled to each other, implying the existence of a 1,4-dioxane ring between a stilbene moiety and a phenyl ring.[12−16] On the basis of this observation, it is proposed that compound **1** is a stilbene-phenylpropane with a 1,4-dioxane ring. The linkage of stilbene and phenylpropane units through a 1,4-dioxane bridge was deduced by HMBC NMR experiments (Figure 1). Thus, after optimizing the J value [$^{2,3}J$(C,H)] for

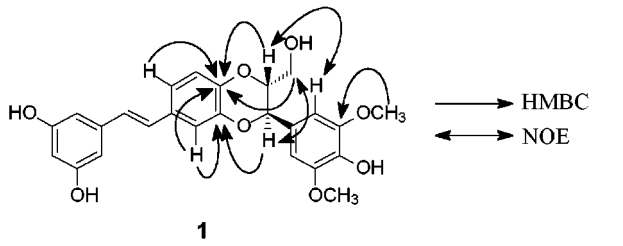

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Figure 1. Selected HMBC and NOE correlations of **1**.

a long-range correlation to 4 Hz, the HMBC cross-peaks for H-2/C-8a and H-3/C-4a were observed. Also, a long-range correlation between the methoxyl signal and C-3′ indicated the position of this methoxyl group as C-3′. The relative trans stereochemistry of the dioxane moiety was confirmed by J value comparison and from the NOESY NMR experiment (Figure 1). Thus, the coupling constant (J = 8.1 Hz) between H-2 and H-3 and a NOE correlation between H-3 and H-2′ clearly indicated a trans configuration of the chiral centers of the dioxane ring.[12−16] Therefore, the structure of this novel stilbenolignan, aiphanol (**1**), was elucidated as 5-[2-[3-(hydroxy-3,5-dimethoxyphenyl)-2-hydroxymethyl-2,3-dihydrobenzo[1,4]dioxin-6-yl]vinyl]benzene-1,3-diol. There are several reports of natural compounds which have a dioxane moiety.[12−16] To the best of our knowledge, aiphanol (**1**) represents the first example of a stilbenolignan linked through a dioxane bridge.

All of the isolates obtained were evaluated for their potential to inhibit cyclooxygenase-1 and -2 (COX-1 and COX-2). Assays were performed according to established protocols.[2,17] Aiphanol (**1**) and isorhapontigenin (**2**) demonstrated IC_{50} values of 1.9 and 1.5 μM, respectively, when evaluated with COX-1, and 9.9 and 6.2 μM, respectively, when evaluated with COX-2. Piceatannol (**3**), the demethyl derivative of **2**, and luteolin were inactive (IC_{50} values >100 μg/mL) in both the COX-1 and COX-2 inhibition assays.

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(10) The seeds of *A. aculeata* were collected in Peru in July 1999 by J. Schunke Vigo, J. G. Graham, and F. Cabieses and dried. A voucher specimen has been deposited at the Field Museum of Natural History, Chicago, IL (accession no. 2222531).

(11) Aiphanol (**1**): brown powder; $[\alpha]^{20}_D$ −21.8° (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ϵ) 233 (5.37), 322 (5.32) nm; CD (MeOH) nm $\Delta\epsilon_{204}$ +16.9, $\Delta\epsilon_{208}$ −13.1, $\Delta\epsilon_{358}$ −7.8, $\Delta\epsilon_{379}$ +7.4; ^{1}H NMR (Me_2CO-d_6, 500 MHz) δ 3.53 (1H, dd, J = 4.1, 12.3 Hz, CH_2OH), 3.74 (1H, dd, J = 2.3, 12.4 Hz, CH_2OH), 3.86 (3H, s, OCH_3), 4.14 (1H, m, H-3), 4.97 (1H, d, J = 8.1 Hz, H-2), 6.28 (1H, brt, J = 1.9 Hz, H-14), 6.56 (2H, d, J = 2.0 Hz, H-12), 6.84 (2H, s, H-2′), 6.90 (1H, d, J = 8.3 Hz, H-5), 6.94 (1H, d, J = 16.4 Hz, H-9), 7.02 (1H, d, J = 16.3 Hz, H-10), 7.08 (1H, dd, J = 1.9, 8.4 Hz, H-6), 7.13 (1H, d, J = 1.9 Hz, H-8); ^{13}C NMR (Me_2CO-d_6, 125 MHz) δ 56.7 (OCH_3), 61.9 (CH_2OH), 77.5 (C-2), 79.7 (C-3), 102.8 (C-14), 105.8 (C-12), 106.1 (C-2′), 115.4 (C-8), 117.8 (C-5), 120.9 (C-6), 128.07 (C-9), 128.10 (C-1′), 128.7 (C-10), 131.8 (C-7), 137.3 (C-4′), 140.6 (C-11), 144.5 (C-4a), 145.1 (C-8a), 148.8 (C-3′), 159.6 (C-13); FABMS m/z 452 $[M^{\bullet}]^+$, 307 (60), 289 (35), 154 (90), 137 (100), 107 (65); HRFABMS m/z $[M^{\bullet}]^+$ 452.1462 (calcd for $C_{25}H_{24}O_8$ 452.1471); HRAPCITOFMS m/z $[M + H]^+$ 453.1546 (calcd for $C_{25}H_{25}O_8$ 453.1549).

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quist, Mass Spectrometry Facility, Department of Chemistry, University of Minnesota, Minneapolis, MN, for the TOF and FAB mass spectral data, respectively. We are grateful to the Research Resources Center, UIC, for the provision of certain spectroscopic equipment used in this investigation. This work was supported by program project No. P01 CA48112 funded by the National Cancer Institute, NIH, Bethesda, MD.

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