NATURAL PRODUCT COMMUNICATIONS

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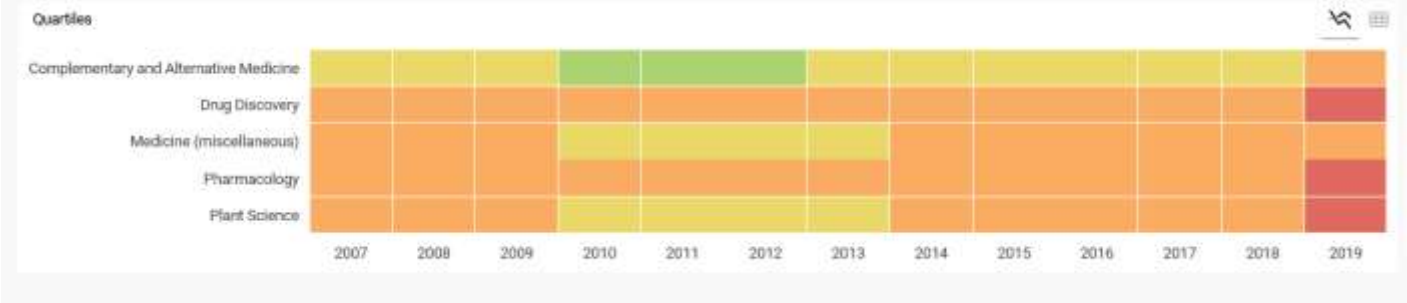
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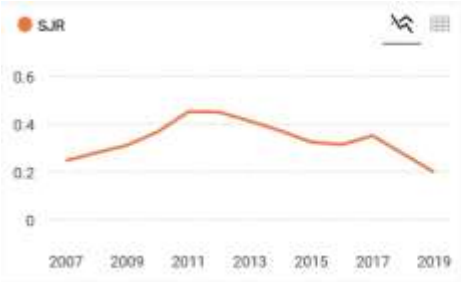
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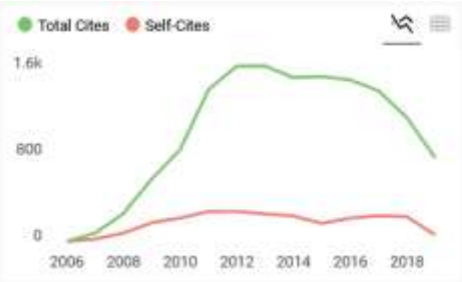
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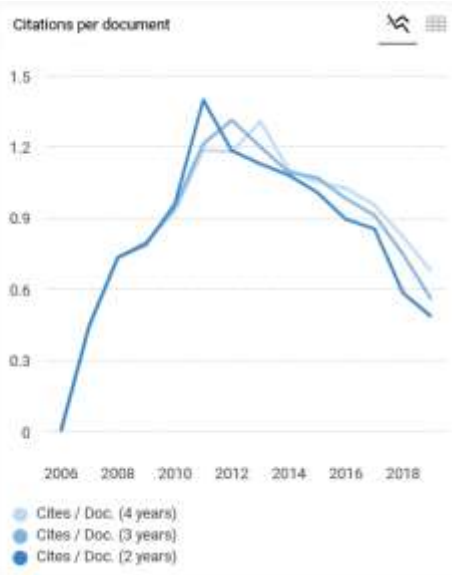
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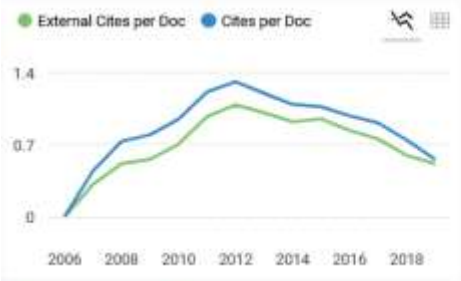
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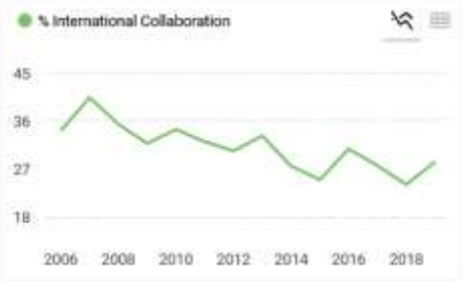
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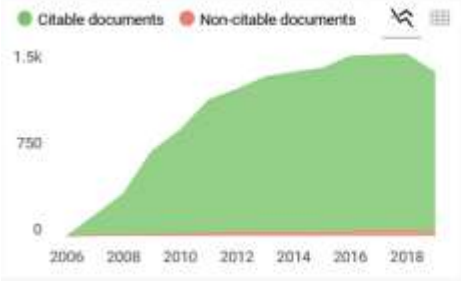
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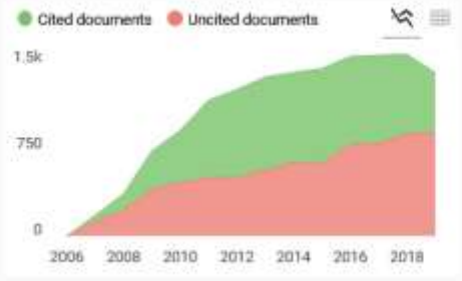
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Melidianolic Acid A and B, New Antimalarial Acyclic Diterpenes from *Aphanamixis grandifolia*

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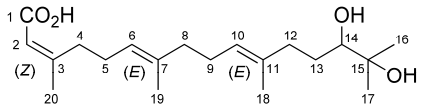
Two new acyclic diterpenes, melidianolic acids A (**1**) and B (**2**), have been isolated from the bark of *Aphanamixis grandifolia*. Their structures were elucidated on the basis of spectroscopic and chemical methods. Melidianolic acids A (**1**) and B (**2**) showed antimalarial activity against *Plasmodium falciparum* 3D7 with IC_{50} of 6.1 and 7.3 μg/mL, respectively.

Keywords: *Aphanamixis grandifolia*, melidianolic acids A and B, acyclic diterpene, antimalarial activity, *Plasmodium falciparum* 3D7.

The Meliaceae is a flowering plant of mostly trees, and shrub and a few herbaceous plants, native to tropical and subtropical regions. Most species, comprising about 50 genera and 550 species, are verger, but some are deciduous [1]. Meliaceae is of particular interest because of the presence of abundance and structural diversity of the highly oxygenated tetranortriterpenoids, limonoids, with a range of biological activities such as insecticidal, insect antifeedant, antibacterial, antifungal, antimalarial, anticancer, and antiviral activities [1]. Some plants belonging to Meliaceae have traditionally been employed as fish or dart arrow poisons, and afforded a several toxic components [2,3].

Aphanamixis grandifolia is a timber tree occurring in Java, Indonesia, and produces poisonous fruits. The peel and seeds of *A. grandifolia* were known to contain sesquiterpenes [4] and limonoids [5-7], which have inhibited the growth of the P388 cell line [7]. Our continuing search for biogenetically interesting compounds from *A. grandifolia* led to isolation of two new acyclic diterpenes, melidianolic acids A (**1**) and B (**2**). This paper describes the isolation and structure elucidation of **1** and **2** as well as antimalarial activity against *Plasmodium falciparum* 3D7.

The bark of *A. grandifolia*, which were collected at Alas Purwo, Indonesia, was extracted with MeOH, and then partitioned between hexane, EtOAc, *n*-BuOH, and water. The EtOAc extract was chromatographed over silica gel eluted with hexane-EtOAc and then $CHCl_3$-MeOH. The



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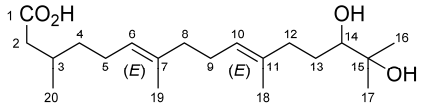

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$CHCl_3$-MeOH fraction was further separated by using an ODS column and C_{18} HPLC to give melidianolic acids A (**1**, 22.8 mg) and B (**2**, 6.5 mg).

The ESIMS of melidianolic acid A (**1**) showed the pseudomolecular ion peak at *m/z* 339 $(M + H)^+$ and the molecular formula, $C_{20}H_{34}O_4$, was established by HRESIMS (*m/z* 339.2524 $(M + H)^+$, Δ -1.1 mmu). IR absorptions implied the presence of hydroxyl (3410 cm^{-1}) and carbonyl (1695 cm^{-1}) functionalities. ^1H and ^{13}C NMR data were shown in Table 1. The ^{13}C NMR and HSQC spectra revealed 20 carbon signals due to one carbonyl carbon, three sp^2 quaternary carbons, three sp^2 methines, one sp^3 quaternary carbon, one sp^3 methine, six sp^3 methylenes, and five methyl groups.

The gross structure of **1** was elucidated by analysis of 2D NMR data including ^1H-^1H COSY, HSQC, and HMBC spectra in Figure 1. ^1H-^1H COSY spectrum of **1** revealed three partial structures **a** (C-4 to C-6), **b** (C-8 to C-10), and

Table 1: ^{1}H and ^{13}C NMR Data for Melidianolic Acids A (**1**) and B (**2**) in $CDCl_3$ at 300 K[a].

	1		**2**	
Position	δ_H (int.; mult.; *J* (Hz))	δ_C	δ_H	δ_C
1		170.3		177.1
2a	5.69 (1H, s)	116.0	2.14 (1H, m)	34.9
2b	2.31 (1H, m)			
3		162.5	2.01 (1H, m)	25.1
4a	2.63 (1H, m)	33.2	1.25 (1H, m)	29.6
4b	2.73 (1H, m)		1.97 (1H, m)	
5	2.19 (2H, m)	26.3	2.10 (2H, m)	25.8
6	5.12 (1H, t, 8.0)	123.6	5.09 (1H, t, 8.0)	124.5
7		135.2		135.2
8	2.01 (2H, m)	39.3	2.06 (2H, m)	39.3
9	2.09 (2H, m)	25.8	2.09 (2H, m)	25.8
10	5.16 (1H, t, 8.0)	124.8	5.16 (1H, t, 8.0)	124.7
11		134.6		135.5
12a	2.06 (1H, m)	36.6	2.03 (1H, m)	36.9
12b	2.25 (1H, m)		2.28 (1H, m)	
13a	1.41 (1H, m)	29.7	1.42 (1H, m)	29.3
13b	1.59 (1H, m)		1.61 (1H, m)	
14	3.36 (1H, brd, 12.0)	78.1	3.37 (1H, brd, 12.0)	78.4
15		73.4		73.3
16	1.20 (3H, s)	26.3	1.22 (3H, s)	26.3
17	1.16 (3H, s)	23.2	1.17 (3H, s)	23.1
18	1.59 (3H, brs)	15.9	1.59 (3H, brs)	15.8
19	1.59 (3H, brs)	15.9	1.60 (3H, brs)	15.8
20	1.91 (3H, s)	25.3	0.97 (3H, d, 6.4)	19.5

[a] δ in ppm.

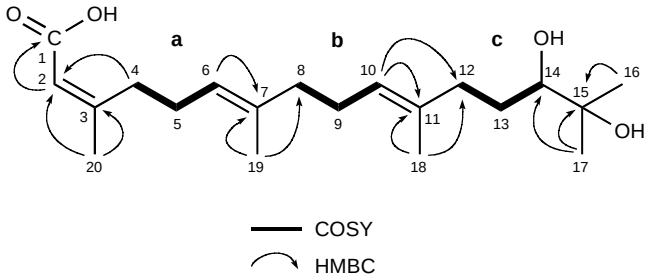

Figure 1: Selected 2D NMR Correlations for Melidianolic Acid A (**1**).

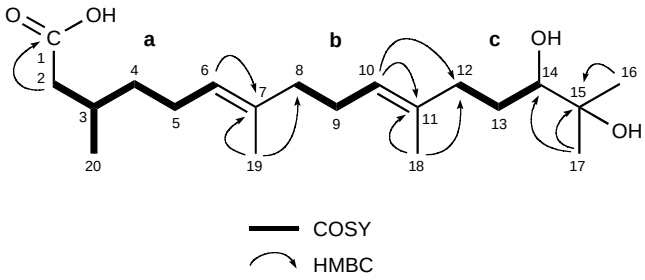

Figure 2: Selected 2D NMR Correlations for Melidianolic Acid B (**2**).

c (C-12 to C-14). Connection of the partial structures **a** and **b** through C-7 was unambiguously established by HMBC correlations for H-6 and H_3-19 to C-7 (δ_C 135.2) and H_3-19 to C-8 (δ_C 39.3). The partial structures **b** and **c** were connected to C-11 on the basis of HMBC correlations for H-10 and H_3-18 to C-11 (δc 134.6) and C-12 (δ_C 36.6). The isopropanol function was connected to C-14 on the basis of HMBC cross-peaks for H_3-17 and H_3-16 to C-15 (δ_C 73.4) and H_3-17 to C-14 (δ_C 78.1). The connectivity between among C-2 and C-4 through C-3 were implied by HMBC correlations for H-4 and H_3-20 to C-2 (δc 116.0). The presence of a conjugated carboxylic acid was verified by a HMBC correlation for H-2 to C-1 (δ_C 170.3). Methylation of **1** with trimethylsilyl diazomethane to afford a methylated derivative supported the presence of a carboxylic acid function. The geometry of the double bonds was determined as 6*E* and 10*E* by comparison of the ^{1}H and ^{13}C chemical shifts with similar compounds [8-10]. Remaining geometry at C-2 was elucidated as *Z* by the NOESY correlation of H_3-20/H-2. Thus, the gross structure of melidianolic acid A was assigned to be **1**.

Melidianolic acid B {**2** $[\alpha]_D^{20}$ -12 (*c* 1.0, MeOH)} showed the pseudomolecular ion peak at *m/z* 341 $(M + H)^+$ in the ESIMS, and the molecular formula, $C_{20}H_{36}O_4$, was established by HRESIMS [*m/z* 341.2511, $(M + H)^+$, Δ -1.1 mmu]. The molecular formula of melidianolic acid B (**2**) was larger than that of **1** by H_2 unit. IR absorptions implied the presence of hydroxyl (3400 cm^{-1}) and carbonyl (1710 cm^{-1}) functionalities. ^{1}H and ^{13}C NMR chemical shifts of **2** were analogous to those of **1** with four methyl groups at C-16, C-17, C-18, and C-19 although signals of trisubstituted olefin carbons (δ_H 5.69; δ_C 116.0 and 162.5) at C-2 and C-3 of **1** were not observed for **2** (Table 1). The gross structure of **2** was elucidated by 2D NMR (^{1}H-^{1}H COSY, HSQC, and HMBC) data (Figure 2). The presence of a carboxylic group was verified by a HMBC correlation for H_2-2 to C-1 (δ_C 177.1), which was also supported by methylation of **2** according to the same procedure as in **1**. The geometry of the double bonds was determined as 6*E* and 10*E* by comparison of the chemical shifts of the ^{1}H and ^{13}C NMR spectra of similar compounds [8-10]. Thus **2** was elucidated to be melidianolic acid B, which was 2,3-dihydro from of **1**.

Melidianolic acids A (**1**) and B (**2**) showed in vitro antiplasmodial activity against *P. falciparum* 3D7 (IC_{50} 6.1 and 7.3 μg/mL, respectively), whereas both of them showed no cytotoxicity (IC_{50} > 100 μg/mL). An acyclic diterpene, glaucaic acid, from *Knema glauca* (Myristicaceae), did not show antimalarial activity against *P. falciparum* [11]. Although recently acyclic triterpenes from *Ekebergia capensis* (Meliaceae) showed in vitro and in vivo antimalarial activities [12], it is the first report on the presence of antimalarial acyclic diterpenes from Meliaceae.

Experimental

General Experimental Procedures: Optical rotations were measured on a JASCO DIP-1000 automatic digital polarimeter. UV spectra were obtained on an Ultrospec 2100 pro spectrophotometer, and IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. 1D and 2D NMR spectra were recorded on a Bruker AV 400 spectrometer, and chemical shifts were referenced to the residual chloroform-*d* (δ_H 7.26 and δ_C 77.0). Standard pulse sequences were employed for the 2D NMR experiments. ^{1}H–^{1}H COSY spectrum was measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1K data points for each of 256 t_1 increments. For HSQC spectra in the phase sensitive mode and HMBC spectra, a total of 256 increments of 1K data points were collected. For HMBC spectra with Z-axis PFG, a 50 ms delay time was used for long-range C–H coupling. Zero-filling to 1K for *F*1 and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation. High-resolution ESI MS were obtained on a LTQ Orbitrap XL (Thermo Scientific).

Plant Material: *Aphanamixis grandifolia* (Meliaceae) were collected at Alas Purwo, East Java, Indonesia in 2007. The botanical identification was made by Ms. Suri, Purbodadi Botanical Garden, Indonesia. A voucher specimen (no. AP070905) is deposited at the Herbarium of Purbodadi Botanical Garden, Indonesia.

Extraction and Isolation: The bark of *A. grandifolia* was extracted with MeOH (10 L x 3). MeOH extracted (126.3 g) was partitioned between hexane, EtOAc, *n*-BuOH, and water. The EtOAc soluble materials (16.7 g) were subjected to a silica gel column (hexane/EtOAc, 1:0 → 5:5, and then $CHCl_3$/MeOH 20:1 → 0:1). The fraction eluted with $CHCl_3$/MeOH (9:1) was applied to an ODS column (10% MeOH→MeOH), in which a fraction eluted with 80% MeOH was purified with an ODS HPLC (55% CH_3CN/0.1% TFA) to afford melidianolic acids A (**1**, 22.8 mg, 0.0016% yield) and B (**2**, 6.5 mg, 0.0004% yield).

Melidianolic Acid A (**1**)

colorless solid.

$[\alpha]_D^{20}$: −18 (*c* 1.0, MeOH).

IR (neat): 3410, 2970, 1695, 1170 cm^{-1}.

^{1}H and ^{13}C NMR: Table 1.

ESIMS (pos.): *m*/*z* = 339 $[M + H]^+$.

HRESITOFMS: *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{35}O_4$: 339.2535; found: 339.2524.

Melidianolic Acid B (**2**)

colorless solid.

$[\alpha]_D^{20}$: −12 (*c* 1.0, MeOH).

IR (neat): 3400, 2930, 2855, 1710 cm^{-1}.

^{1}H and ^{13}C NMR: Table 1.

ESIMS (pos.): *m*/*z* = 363 $[M + Na]^+$.

HRESITOFMS: *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{36}O_4Na$: 363.2511; found: 363.2504.

Antiplasmodial activity: Human malaria parasites were cultured according to the method of Trager et al. [13] The antimalarial activity of the isolated compounds was determined by the procedure described by Budimulja et al. [14] In brief, stock solutions of the samples were prepared in DMSO (final DMSO concentrations of < 0.5%) and were diluted to the required concentration with complete medium (RPMI 1640 supplemented with 10% human plasma, 25 mM HEPES and 25 mM $NaHCO_3$) until the final concentrations of samples in culture plate wells were 10; 1; 0.1; 0.01; 0.001 μg/mL. The malarial parasite *P. falciparum* 3D7 clone was propagated in a 24-well culture plates. Growth of the parasite was monitored by making a blood smear fixed with MeOH and stained with Geimsa stain. The antimalarial activity of each compound was expressed as an IC_{50} value, defined as the concentration of the compound causing 50% inhibition of parasite growth relative to an untreated control. The percentage of growth inhibition was expressed according to following equation : Growth inhibition % = 100- [(test parasitaemia/control parasitemia) × 100. Chloroqine: IC_{50} 0.011 μM.

Cytotoxic Activity: A549 (human lung adenocarcinoma epithelial cell line) was seeded onto 96-well microtiter plates at 5 × 10^3 cells per well. Cells were preincubated for 24 h at 37 °C in a humidified atmosphere of 5% CO_2. Different concentrations of each compound (10 μL) were added to the cultures, and then the cells were incubated at 37 °C for 48 h. On the third day, 15 μL MTT solution (5 mg/mL) was added into each well of the cultured medium. After further 2 hours of incubation, 100 μL of 10% SDS-0.01 N HCl solution was added to each well and the formazan crystals in each well were dissolved by stirring with a pipette. The optical density measurements were made using a micropipette reader (Benchmark Plus microplate spectrometer, BIO-RAD) equipped with a two wavelengths system (550 and 700 nm). In each experiment, three replicate of wells were prepared for each sample. The ratio of the living cells was determined based on the difference of the absorbance between those of samples and controls. These differences are expressed in percentage and cytotoxic activity was indicated as an IC_{50} value. Taxol: IC_{50} 0.0014 μM.

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