

Chem Vitex

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Submission date: 26-Jun-2020 06:57AM (UTC+0700)

Submission ID: 1349738030

File name: jurnal_Chem_Vitex_faradiba.docx (437.61K)

Word count: 2668

Character count: 14830

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A Novel Clerodane Diterpene from *Vitex cofassus*

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Received September 29, 2016; accepted October 30, 2016

New clerodane diterpene, 16-hydroxy-pentandralactone (**1**) and known diterpene acuminolide (**2**) were isolated from the methanol extract of *Vitex cofassus* leaves. The chemical structure and the absolute configuration of **1** were determined by MS, NMR and electron circular dichroism (ECD) experiments. The isolated compounds were evaluated for their antiproliferative activities against a panel of human tumor cell lines, including a multidrug-resistant (MDR) cell line. Both compounds showed potent antiproliferative activities against all the tested cell lines with IC₅₀ values of 5.4–11.4 μM. Their effects on cell viability were also tested using vascular endothelial growth factor (VEGF)-stimulated human umbilical vein endothelial cells (HUVECs). Compound **1** inhibited VEGF-stimulated HUVEC proliferation in a dose-dependent manner. Based on these results, compound **1** could be a candidate for antitumor agent and inhibitor of angiogenesis.

Key words *Vitex cofassus*; clerodane diterpene; antiproliferative activity; antiangiogenic activity

The genus *Vitex* belongs to the family Lamiaceae and is distributed around the world.¹⁾ It has been used as folk medicine in Asia and Europe for the treatment of female hormonal disorders, headache, diarrhea, and other conditions. However, among the more than 250 species of *Vitex*, only 24 have been investigated for their phytoconstituents according to a literature search conducted up to 2013.¹⁾ Terpenes, flavonoids, and lignans are the main constituents isolated from *Vitex* species.^{2–5)} Diverse pharmacological activities, including hepatoprotective,⁶⁾ antitumor,^{7–9)} antimicrobial,²⁾ antimutagenic,¹⁰⁾ anti-inflammatory,¹¹⁾ anti-human immunodeficiency virus (HIV),¹²⁾ and antitubercular¹³⁾ activities, have also been reported. *Vitex cofassus*, native to New Guinea and the Southwest Pacific Islands, is an untouched plant, although a pharmacotoxicological study of the crude extract of its bark was conducted in 1969.¹⁴⁾

We found that the methanol extract of this plant displayed potent cell growth inhibitory activity in several human tumor cell lines. Herein we describe the isolation and structure elucidation of novel diterpenoid (**1**), together with known acuminolide (**2**)^{15,16)} from *V. cofassus* (Fig. 1). We also report their antiproliferative activities against human tumor cell lines as well as human umbilical vein endothelial cells (HUVECs) stimulated by vascular endothelial growth factor (VEGF).

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Results and Discussion

Compound **1** was obtained as a yellowish syrup. Its molecular formula was determined to be C₂₀H₂₈O₅ from the [M+H]⁺

peak at *m/z* 349.2017 (Calcd for 349.2015) in the high resolution (HR)-FAB-MS spectra. The IR spectrum of **1** showed absorption bands corresponding to hydroxyl (3016 cm^{−1}), α,β-unsaturated aldehyde (1651 cm^{−1}), and α,β-unsaturated γ-lactone carbonyl (1759 cm^{−1}) groups. The ¹³C-NMR experiment indicated the presence of twenty carbons, including an aldehyde carbon at δ_C 188.9, three strongly deshielded sp² carbons at δ_C 175.6, 172.0, and 170.9, an alkenyl carbon at δ_C 117.3, a hemiacetal carbon at δ_C 98.3, and four methyl groups at δ_C 18.7, 17.3, 16.2, and 9.6 (Table 1). The ¹H-NMR spectrum showed one olefinic methyl at δ_H 2.07 (3H, brs, CH₃-18), two tertiary methyls at δ_H 0.912 (3H, s, H-19) and 0.902 (3H, s, H-20), as well as a secondary methyl at δ_H 0.896 (3H, d, *J* = 7.2 Hz, H-17). An aldehydic proton at δ_H 9.97, which formed a bond with the carbon at δ_C 188.9 as shown by the results of ¹H-detected heteronuclear multiple quantum coherence (HMQC) experiment, was also observed. The heteronuclear multiple bond correlation (HMBC) connectivity of H-3 with C-1 and C-2 confirmed the presence of an α,β-unsaturated aldehyde function. Further HMBC analysis revealed the location of two methyl moieties as CH₃-17 showed correlations of

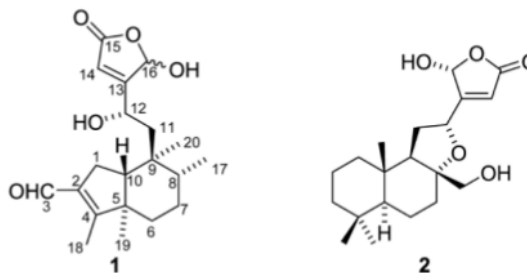


Fig. 1. Compounds Isolated from Leaves of *Vitex cofassus*

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Table 1. NMR Data for Compound 1^{a)}

No.	δ_{H}	δ_{C}	No.	δ_{H}	δ_{C}
1	2.11, 2.45 (2H, m)	26.6	11	1.58, 1.74 (2H, m)	45.0
2		137.8	12	4.72 (1H, br s)	65.6
3	9.97 (1H, s)	188.9	13		170.9
4		172.0	14	5.98 (1H, br s)	117.3
5		51.6	15		175.6
6	1.45 (1H, td, 12.6, 4.2), 1.70 (1H, dt, 12.0, 3.3)	34.7	16	6.24 (1H, s)	98.3
7	1.53 (2H, m)	30.4	17	0.896 (3H, d, 7.2)	16.2
8	2.18 (1H, m)	38.6	18	2.07 (3H, br s)	9.6
9		39.5	19	0.97 (3H, s)	17.3
10	1.89 (1H, dd, 11.4, 5.4)	54.7	20	0.902 (3H, s)	18.7

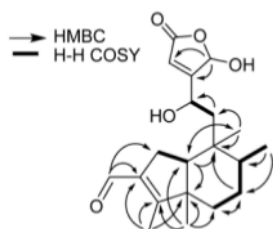
^{a)} ¹H-NMR: 600 MHz, ¹³C-NMR: 150 MHz in (CD₃)₂CO.

Fig. 2. Selected HMBC and COSY Correlations of 1

C-7 with C-8, and of CH₃-20 with C-9, C-10, and C-11. The above observations suggested that compound 1 possessed 4(3→2)-*abeo*-clerodane as the parent structure. The existence of a γ -hydroxyl butenolide group was assumed from the presence of signals assignable to the hemiacetal carbon at δ_{C} 98.3 (C-16), two sp^2 carbons at δ_{C} 170.9 (C-13) and δ_{C} 117.3 (C-14), and a carbonyl carbon at δ_{C} 175.6 (C-15). These chemical shifts were very similar to those of clerodane diterpenes with a γ -hydroxyl butenolide group.^{17–19} The connection between the hexahydroindene skeleton and the hydroxyl butenolide group was assisted by a two-atom aliphatic chain whose signals appeared as cross peaks between H-11 and H-12 in ¹H–¹H correlation spectroscopy (COSY) and of H-20 with C-11 in HMBC experiment (Fig. 2). This connection was also supported by the molecular formula as mentioned above.

¹H- and ¹³C-NMR experiments also revealed similarity to pentandralactone isolated from *Callicarpa petandra*.²⁰ Comparison of the MS spectra of compound 1 and pentandralactone indicated the existence of an additional hydroxyl group in 1. Major NMR spectral differences in benzene-*d*₆ between the two compounds were noted for the proton and the carbon at 16-position. The assignable signals for H-16 and C-16 of compound 1 were downfielded to around 6.24 ppm (1H, s) and δ_{C} 98.3, respectively, while those of pentandralactone appeared at δ_{H} 4.82 (2H, d) and δ_{C} 70.2, respectively.²⁰ These observations also indicated that the additional hydroxyl moiety was attached to C-16 position. Based on the comparison of the calculated and experimental electron circular dichroism (ECD) spectra, the absolute configuration was deduced as 5*R*, 8*R*, 9*S*, 10*R*, and 12*S* (Fig. 3). We assumed that the configuration of a hemiacetal moiety at C-16 was approximately 4:1 mixture of *R* and *S* from the ECD analysis (Fig. 3) and ¹³C-NMR observation (Fig. S2 in Supplementary materials). Accordingly, compound 1 was

identified as (3*aR*,6*R*,7*S*,7*aR*)-7-[(*S*)-2-hydroxy-2-[(*R*&*S*)-2-hydroxy-5-oxo-2,5-dihydrofuran-3-yl]ethyl]-3*a*,6,7-tetramethyl-3*a*,4,5,6,7,7*a*-hexahydro-1*H*-indene-2-carbaldehyde (IUPAC), namely 16-hydroxy-pentandralactone.

Clerodane possessing cyclopentene carbaldehyde ring-A as a result of a (4→2) rearrangement is a rare natural skeleton, and compounds having such a structure were isolated from *Ca. pentandra*,²⁰ *Polyalthia longifolia*,^{21–23} *Solidago altissima*,^{24,25} and *Clausena dunniana*.²⁶ It should be noted that this is the first isolation of clerodane with rearranged ring-A from *Vitex* species.

Compound 2 was identified as acuminolide by comparison of spectral data with those previously reported in the literature.^{15,16}

Antiproliferative Activities Isolated compounds 1 and 2 were evaluated for their antiproliferative activities against the following human tumor cell lines: lung carcinoma (A549), epidermoid carcinoma (KB), vincristine-resistant KB subline (KB-VIN), triple-negative breast cancer (MDA-MB-231), and estrogen receptor-positive breast cancer (MCF-7). Both compounds displayed significant activities against all the tested tumor cell lines, and the IC₅₀ values ranged from 5.4 to 11.4 μM (Table 2). Interestingly, they were effective against KB-VIN, a P-glycoprotein (P-gp)-overexpressing multidrug-resistant (MDR) cell line.

Antiangiogenic Activities VEGF is a critical regulator of tumor angiogenesis. VEGF-stimulated HUVECs have been widely used in preliminary assays for antiangiogenic activity. Compound 1 inhibited VEGF-stimulated HUVEC proliferation in a dose-dependent manner, suggesting that 1 might have antiangiogenic activity without showing cytotoxicity to HUVECs even at 30 μM (Fig. 4). Although 0.3 μM of acuminolide (2) also inhibited the VEGF-stimulated HUVEC proliferation, cell viability was reduced to 47% when 3 μM of 2 was used. These observations suggest that 2 is cytotoxic to normal cells.

Experimental

General Experimental Procedures NMR spectra were measured on a JNM-ECS400 or JNM-ECA600 spectrometer with tetramethylsilane as the internal standard. Mass spectral measurements were carried out on a JEOL JMS-700 mass spectrometer or a JEOL JMS SX-102. Optical rotations were measured on a JASCO P-2200 digital polarimeter. CD spectra were measured on JASCO J-820 spectrometer. Flash column chromatography was conducted on a Biotage SNAP cartridge

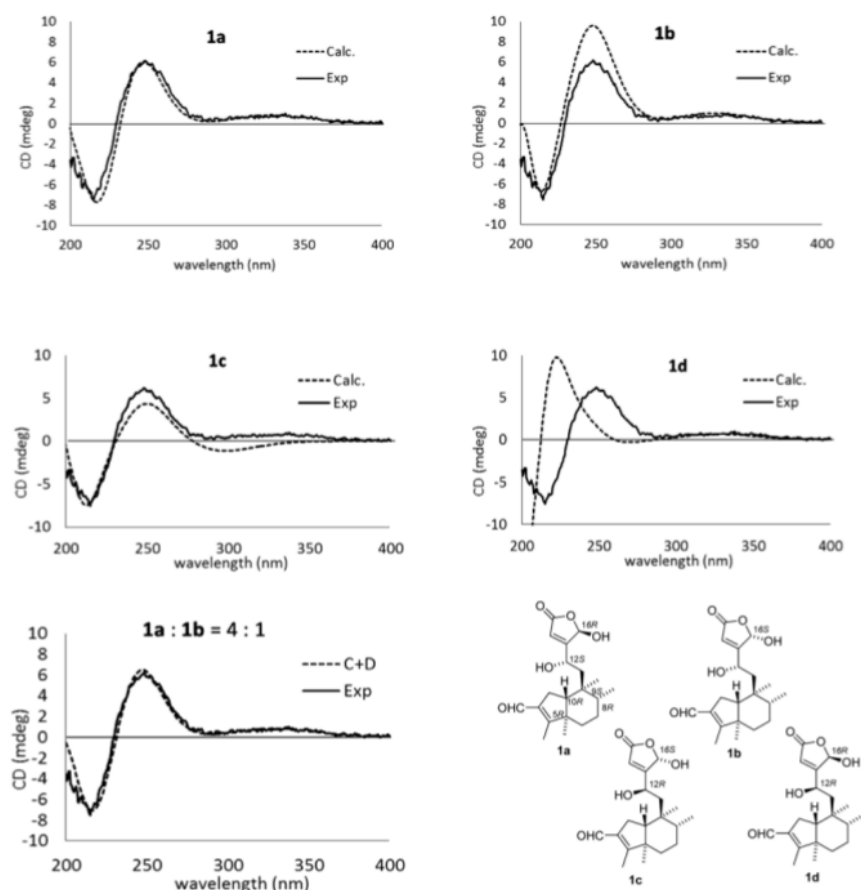


Fig. 9. Calculated and Experimental ECD Spectra of **1** in Acetonitrile

The experimental electron circular dichroism (ECD) spectrum (solid line) of **1** was the closest to the calculated ECD spectrum of (5*R*, 8*R*, 9*S*, 10*R*, 12*S*, 16*R*) isomer **1a** (dashed line). The best matched spectrum was observed when **1a** and **b** were mixed at a 4 : 1 ratio.

Table 2. Antiproliferative Activities of Isolated Compounds

Cmpd.	Tumor cell line ^{a)} (IC ₅₀ μM) ^{b)}				
	A549	MDA-MB-231	MCF-7	KB	KB-VIN
1	10.0	6.4	11.0	9.9	11.4
2	6.5	5.4	8.9	7.4	8.4
1 PTX ^{c)} (nM)	5.8	6.4	8.5	5.0	1421.9

a) Human tumor cell lines: lung carcinoma (A549), triple-negative breast cancer (MDA-MB-231), estrogen receptor-positive breast cancer (MCF-7), epidermoid carcinoma (KB), vincristine-resistant KB subline (KB-VIN). b) Antiproliferative activity expressed as IC₅₀, which is the concentration of compound that caused 50% reduction relative to untreated cells as determined by the SRB assay. c) Paclitaxel as experimental control.

using silica gel 60N (63–100 μm) and a Buchi pump controller C-610. Analytical TLC performed on silica gel 60 F254 and RP-18 F254s (Merck Co., Germany). Preparative TLC was conducted on precoated silica gel 60 F254 glass plates (Merck Co.).

Plant Material *Vitex cofassus* was collected in Makassar Province, South Sulawesi, Indonesia in 2013. The specimens were identified by Indonesia Institute of Sciences and a sample (KNG-FD-011) was deposited in the herbarium of Molecular Pharmacognosy Laboratory, Pharmaceutical Science, Kanazawa University, Ishikawa, Japan.

Extraction and Isolation Air-dried and powdered leaves

of *V. cofassus* (2.5 kg) were extracted with MeOH (10.0 L) at room temperature for three days. The extract was concentrated *in vacuo* to obtain a viscous mass (243.0 g), which was partitioned between water and CHCl₃. The aqueous layer was further partitioned between *n*-BuOH and water to yield *n*-BuOH (77.2 g) and water (66.5 g) layers.

The CHCl₃ layer (27.7 g) was subjected to flash column chromatography on silica gel using gradient mixtures of MeOH–CH₂Cl₂ from 1 to 100% as eluent to afford five fractions A–E.

Fraction C (FC, 10.0 g) was selected for further separation on the basis of data from the assay for antiproliferative activity.

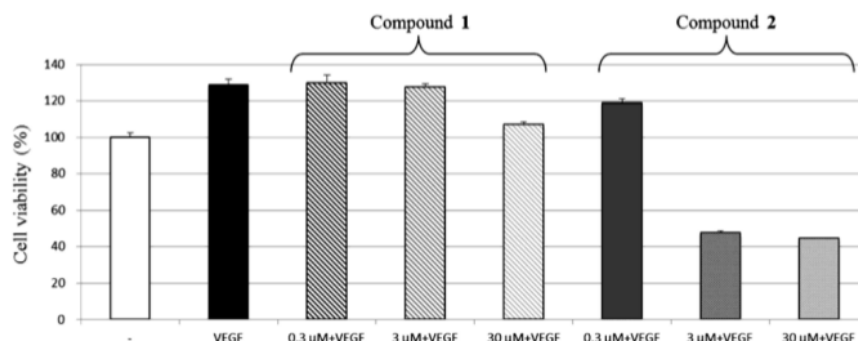


Fig. 4. Antiangiogenesis Activities of Compounds 1 and 2

Effects of compounds 1 and 2 on cell viability (%) of VEGF-stimulated HUVECs are shown. The cells were stimulated with VEGF only, or with VEGF plus compound (0.3–30 μM) for 48 h. Cell viability (%) was determined by using WST-8 solution (10 μL).

Further purification of FC was performed by silica gel flash column chromatography using the same gradient solvent system as that above to obtain eight subfractions (FC1–FC8). Subfraction C5 (FC5) was chromatographed again using gradient mixtures of MeOH–CH₂Cl₂ from 1 to 100% as eluent to obtain nine subfractions (FC51–FC59). Subfraction FC56 was purified by RP-18 preparative TLC (MeOH–H₂O, 3:1) to obtain compound 1 (6.0 mg) and compound 2 (16.5 mg).

16-Hydroxy-pentandralactone (1) [α_D^{25} : +49.0 ($c=0.065$, CHCl₃). *R*_f: 0.4 (RP-TLC, MeOH–H₂O, 3:1). IR (KBr): 3016, 2926, 2856, 1759, 1651, 1213, 775, 754, 735 cm⁻¹. ¹H-NMR (C₆D₆, 600 MHz) δ : 9.69 (1H, s), 6.05 (1H, brs), 6.02 (1H, brs), 4.67 (1H, brs), 2.47 (1H, m), 2.08 (2H, m), 1.73 (1H, dd, 11.4, 5.4), 1.58 (1H, m), 1.50 (3H, brs), 1.43 (1H, m), 1.33 (2H, m), 1.20 (1H, m), 0.97 (3H, d, 6.6), 0.74 (3H, s), 0.64 (3H, s). ¹³C-NMR (C₆D₆, 150 MHz) δ : 189.0, 174.1, 173.1, 171.5, 137.1, 117.2, 97.8, 65.1, 53.9, 51.1, 44.4, 38.9, 38.2, 34.0, 28.8, 26.0, 18.6, 17.1, 16.0, 9.4. ¹H- and ¹³C-NMR in (CD₃)₂CO: Shown in Table 1. HR-FAB-MS: *m/z* [M+H]⁺ Calcd for C₂₀H₂₉O₅: 344.2015. Found: 349.2017.

Calculation of ECD Spectrum The most stable conformer of 1 was predicted using Spartan'14 by a preliminary conformational analysis with the MMFF94 force field followed by geometry optimization using Gaussian09²⁷ with the density functional theory (DFT) B3LYP/6-31G(d). The ECD spectrum in acetonitrile was calculated for the predicted most stable conformer by time-dependent DFT (TDDFT) with the CAM-B3LYP/SVP. The solvent effect was introduced by the polarizable continuum model (PCM). Ten low-lying excited states were calculated. The calculated spectrum was displayed using GaussView 5.0.920 with the peak half-width at half height being 0.333 eV. The calculated spectrum was shifted by +10 nm to match the experimental spectrum.

Assay for Antiproliferative Activity Antiproliferative activity of the compounds was determined by the sulforhodamine B (SRB) assay as described previously.²⁸ Briefly, all cell lines were grown in T-75 flasks at 37°C with 5% CO₂ in air. Freshly trypsinized cell suspensions were seeded on 96-well microtiter plates at the density of 4000–3000 cells per well and treated with the compounds. After a 72-h culture with the compounds, the cells were fixed in 10% trichloroacetic acid and then stained with 0.04% SRB. The absorbance at 515 nm was measured using a microplate reader (ELx800, BioTek) operated by Gen5 software (BioTek) after solubilizing the bound

dye with 10 mM Tris base. Then, IC₅₀ was calculated for at least three independent experiments performed with duplication, and IC₅₀ values were calculated statically (MS Excel). The following human tumor cell lines were used: lung carcinoma (A549), triple-negative breast cancer (MDA-MB-231), estrogen receptor-positive breast cancer (MCF-7), KB (originally isolated from epidermoid carcinoma of the nasopharynx), and KB-VIN (vincristine-resistant KB subline showing DR phenotype by overexpressing P-gp). All the cell lines were obtained from the Lineberger Comprehensive Cancer Center (UNC-CH) or from ATCC (Manassas, VA, U.S.A.), except KB-VIN, which was a generous gift from Professor C. Cheng (Yale University, U.S.A.). The cells were cultured in RPMI-1640 medium supplemented with 2 mM L-glutamine and 25 mM N-(2-hydroxyethyl)piperazine-N'-2-ethanesulfonic acid (HEPES, CORNING) supplemented with 10% heat-inactivated fetal bovine serum (Hyclone), 100 μg/mL streptomycin, and 100 IU penicillin (CORNING). KB-VIN was maintained in the presence of 100 nM vincristine. Paclitaxel (PTX) was used as experimental control.

Antiangiogenesis Assay The assay was performed by cell viability assay using a Cell Counting Kit-8.²⁹ HUVECs (2500 cells) were seeded on a 96-well plate for 24 h, and treated with VEGF and the compound. After 48 h, 10 μL of WST-8 solution was added, and cells were kept for 40 min at 37°C. The absorbance was measured at 450 nm.

Acknowledgments The authors thank the Ministry of Research, Technology and Higher Education of Indonesia for the DIKTI scholarship grant. This study was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan awarded to K.N.G. (Grant No. 25293024). Theoretical calculations were partly performed in the Research Center for Computational Science, Okazaki, Japan.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials, one- and two-dimensional (1- and 2D)-NMR spectra for the new compound 1.

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