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Parvidepsidone, a Novel Depsidone from the Barks of *Garcinia parvifolia* Miq.

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Abstract – *Garcinia parvifolia* Miq., belongs to *Garcinia* genus and Clusiaceae family, is one of the well-known species from *Garcinia* genus which widely found in tropical and subtropical countries, and has been reported to contain natural bioactive compounds. A novel depsidone, parvidepsidone (**2**), was isolated from the barks of *G. parvifolia* along with two known compounds: stigmasterol (**1**) and rubraxhantone (**3**). Based on information of LC-MS, 1D and 2D NMR spectra, the structure of parvidepsidone (**2**) was fully assigned.
Keywords – *Garcinia parvifolia* Miq., Parvidepsidone, Stigmasterol, Rubraxhantone

Introduction

Garcinia parvifolia Miq., belongs to *Garcinia* genus and Clusiaceae family, is one of the well-known species from *Garcinia* genus which is widely distributed in tropical and subtropical countries including Indonesia, Malaysia, Thailand and Brunei. *G. parvifolia* Miq., locally known as "asam kandis", "asam kundong" or cherry mangosteen, has been reported to has several natural bioactive compounds.[1] The genus of Garcia are rich of secondary metabolites such as polyphenols, flavonoids, xanthones, and polyisoprenylated benzophenones.[2-5] Those metabolites were reported to be the ingredients that contribute to the biological capabilities of *G. parvifolia* Miq. including antioxidant,[6] antiviral[7] and antidiabetes.[8] The crude extracts and pure compounds from this plant also were found to be cytotoxic against several cancer cell line, including p388 leukemia cell line,[9] L1219 murine leukemia cell line[10] and human breast cancer cell,[11] thus possessing its potential as anti-carcinogenic agent.

This current study aimed to discover a new compound from the barks of *G. parvifolia* Miq. Column chromatography separation of the *G. parvifolia* crude methanolic backs extract was performed. Additionally, the isolation, structure elucidation, and chemical constituents were also conducted by LC-MS/MS, 1D and 2D NMR analysis. A new depsidone, namely parvidepsidone (**2**), as well as two well-known compounds, stigmasterol (**1**) and rubraxanthone (**3**) were successfully isolated from *G. parvifolia* Miq. barks. (Fig. 1).

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Experimental

General experimental procedures – Melting points were obtained with an electrothermal digital melting point apparatus and was uncorrected. UV spectra were measured on HP 8453A UV-visible spectroscopy systems (Hewlett-Packard, CA, USA), while IR spectra were recorded on a diode array spectrophotometer FTIR Prestige-21 (Shimadzu, Kyoto, Japan). LC-MS analysis to measure molecular weight was performed by using a Hitachi L-6200 Intelligent Pump coupled to a Mariner™ API-TOF Biospectrometry Workstation (Applied Biosystem, CA, USA). Mass spectroscopy measurements were performed on a time-of-flight (TOF). Samples were introduced to MS via electrospray ionization (ESI system) in the positive ion mode. Thin layer chromatography (TLC) was performed using silica gel GF_{254} (TLC sheets, silica-gel-precoated) (Merck, Darmstadt, Germany). Spots were visualized on TLC under UV light at 254 nm using TLC visualizer (CAMAG Scientific Inc., Wilmington, NC). Column chromatography was performed by using silica gel 100 (70-230 Mesh ASTM) (Merck, Darmstadt, Germany) with hexane, EtOAc and MeOH as organic solvents. Samples were subjected to Sephadex LH-20 column and eluted with CH_2Cl_2 and MeOH (1:1, v/v). ^1H NMR, ^{13}C NMR, and correlation NMR spectra including correlation microscopy (COSY), heteronuclear multiple bond correlation (HMBC) and heteronuclear single quantum coherence (HSQC) of compounds in $CDCl_3$ examined

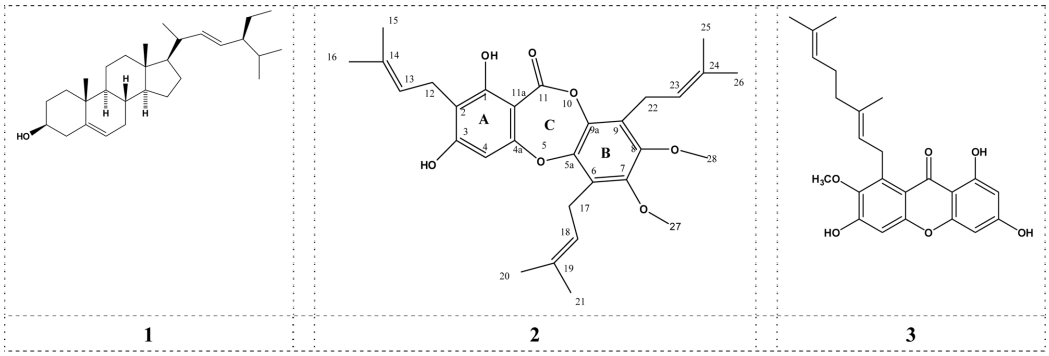


Fig. 1. The structures of compounds (**1 - 3**) isolated from *G. parvifolia* Miq. barks.

Table 1. ^{1}H and ^{13}C NMR data of **2** in $CDCl_3$ (δ in ppm, 500 MHz for ^{1}H and 125 MHz for ^{13}C)

No. C	δ ^{1}H	δ ^{13}C	δ_C HMBC
1	13.80 (OH)	161.91	C-1, C-2
2	-	108.57	
3	6.35 (OH)	160.76	
4	6.32 (3H, *s*)	93.41	C-1; C-2; C4a
4a	-	155.30	
5a	-	152.73	
6	-	135,73	
7	-	156.61	
8	-	147.96	
9	-	114.96	
9a	-	131.77	
11	-	182.87	
11a	-	103.87	
12	3.46 (2H, *d*, *J* = 7.35 Hz)	21.61	C-1; C-2: C13
13	5.30 (1H, *t*, *J* = 7.35 Hz)	121.67	C-16
14	-	122.6	
15	1.77 (3H, *s*)	26.09	C-2; C-13; C-16
16	1.85 (3H, *s*)	18.10	C-2; C-13
17	3.56 (2H, *d*, *J* = 7.35 Hz)	23.20	C-5a; C-7; C-18; C-19
18	5.20 (1H, *t*, *J* = 5.30 Hz)	122.03	C-20; C-21
19	-	132.35	
20	1.85 (3H, *s*)	18.17	C-21
21	1.68 (3H, *s*)	25.95	C-18; C-19; C-21
22	4.11 (2H, *d*, *J* = 6.7)	26.16	C-9; C-9a; C-23; C-24
23	5.24 (1H, *t*, *J* = 5.50 Hz)	123.72	C-22
24	-	135.82	
25	1.87 (3H, *s*)	18.34	-
26	1.69 (3H, *s*)	26.54	-
27	3.96 (3H, *s*)	60.99	C-7
28	3.79 (3H, *s*)	60.81	C-8

Values are in parentheses and reported in Hz; the assignments were based on ^{1}H-^{1}H COSY and HMBC experiments.

using an NMR Spectrometer ECA-500 (Jeol, Tokyo, Japan) operating at 500 MHz (^{1}H) and 125 MHz (^{13}C) with chemical shifts given in ppm (δ).

Plant materials – The barks of *G. parvifolia* (3 kg) were collected in Bulungan Forest, North Kalimantan, Indonesia and identified by Dr. Ismail R. A voucher specimen (#625) of the plant was deposited at the Herbarium Bogoriense, Cibinong, Indonesia.

Extraction and isolation – The air-dried *G. parvifolia* Miq. barks (3.5 kg) were pulverized and extracted with hexane (6 L) quadruplicates at room temperature. The solvent was removed to yield 35.7 g of crude extract. The residue was continued to extract with methanol to yield 374.7 g of methanol crude extract. Separation of the hexane extract (30 g) on a silica gel column chromatography eluted with the mixture of hexane and ethyl acetate (EtOAc) (from 10:0 to 0:10 v/v) obtained 15 fractions (1-15). Fraction 3 (0.89 g) was separated using Sephadex LH-20 column chromatography eluted with hexane-EtOAc to provide compound **1** (600 mg). Fraction 5 (1.333 g) was subjected to Sephadex LH-20 column and eluted with CH_2Cl_2 and methanol (1:1, v/v) to give four sub fractions (F5.1 – F5.4). Sub fraction F5.3 (340 mg) was separated by using chromatotron (centrifugal chromatography) with hexane-EtOAc to afford compound **2** (120 mg). The crude of methanol extract (100 g) was partitioned with EtOAc-water (1:1, v/v) quadruplicates to yield 64.83 g of EtOAc extract. The EtOAc extract (32 g) was fractionated by silica gel column (200 g) and eluted with hexane-EtOAc (from 10:0 to 0:10 v/v), followed by EtOAC-MeOH (from 8:2 to 0:10 v/v) to obtain 18 fractions (1-18). After purification by silica gel radial chromatography eluted with acetone-hexane, compound **3** (64 mg) was obtained from fraction F4 (150 mg).

Stigmasterol (1) – white needles (600 mg). m.p. 138 -140 °C; UV (MeOH) λ_{max} nm: 229; IR (KBr) $_{max}$ cm^{-1}: 3419 – 3294, 2937-2864. ^1H NMR ($CDCl_3$, 500 MHz): δ_H 1.01 (3H, *s*), 1.03 (3H, *s*), 0.84 (3H *d, j* = 3.15 Hz), 0.79 (3H, *d, j* = 5.9 Hz), 0.83 (3H, *d, j* = 5.6 Hz), 0.91 (3H, *dd*), 5.35 (1H, *d. J* = 5.0 Hz, H-6), 5.16 (1 H, *t, J* = 8.4 Hz, H-22), 5.01 (1 H, *t, J* = 8,4 Hz, H-23), 3.52 ppm (1H, *m*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 121.92 (C-6), 138.53 (C-22), 129.43 (C-23), 140.92 (C-5). The comparison of NMR spectra of **1** has similarities to the literature data.[12]

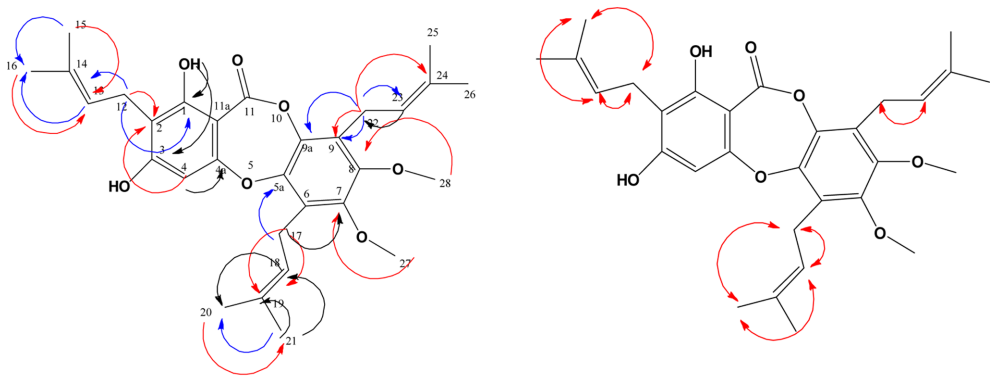
Parvidepsidone (2) – yellow powder (120 mg). UV (MeOH) λ_{max} nm: 216.0, 244.5, 259.5 and 314.0; IR (KBr) $_{max}$ cm^{-1}: 3415 – 1644. Table 1 displays the NMR spectral data of **2**. ESI-MS *m/z* $[M+H^+]$ and $[2M+Na^+]$ calculated for $C_{30}H_{36}O_7$ found 509.12 (cacld 509.25338) and 1039.21 (cacld 1039.48143), respectively.

Rubraxhantone (3) – yellow powder (64 mg). m.p 201-203 °C; UV (MeOH) λ_{max} nm: 217, 240, 310 and 344; IR (KBr) $_{max}$ cm^{-1}: 3424 – 1643. ^1H NMR ($CDCl_3$, 500 MHz): δ_H 13.50 (1H,s, OH), 6.83 (1H, s, H-5), 6.19 (1H, *d, J* = 1.85 Hz, H-2), 6.30 (1H, *d, J* = 1.85 Hz, H-4), 3.79 (3H, s, 11'-OCH_3), 5.27 (1H, *t, J* = 5.5, 1.3 Hz, H-1'), 5.03 (1H, *t*, *J* = 5.5, 1.3 z, H-6), 4.11 (2H, *d, J* = 6.5 Hz, H-2'), 2.05 (2H, m, H-4'), 1.97 (2H, *t, J* = 7.9 Hz, H-5'), 1.52 (3H,s, H-8'), 1.55 (3H, s, H-9'), 1.82 (3H, s, H-10'); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 164.07 (C-3), 26.46 (C-4'), ESI-MS: *m/z* $[M+H^+]$ = 411.08 (calcd 411.18022). The comparison of NMR spectra of **3** has similarities to the literature data.[13]

Result and Discussion

Compounds **1** and **3** were determined by comparing ^1H NMR, ^{13}C NMR and MS spectral data with those in the literature and identified as stigmasterol[12] and rubraxanton,[13] respectively. Compound **2** (parvidepsidone) was isolated as a yellow powder with molecular ion peaks at *m/z* 509.12 (calcd 509.25338) and 1039.21 (cacld 1039.48143), which were confirmed by high-resolution mass spectrometry to be compatible with the chemical formula $C_{30}H_{36}O_7$. The UV-VIS spectrum showed maximum absorption (λ_{max}) at 216.0, 244.5, 259.5 and 314.0, which indicate the presence of an aromatic moiety and a typical UV patter of the depsidone chromophore.[14] The IR ν_{max} (KBr) spectrum of compound **2** indicated the presence of hydroxyl (3415 cm^{-1}) and lactone carbonyl groups (1644 cm^{-1}), indicating the presence of a depsidone chromophore.[15] The ^1H NMR spectrum of **2** (Table 1) reveals protons for one aromatic unit and one hydroxyl group at $_H$ 6.32 (1H, s, H-4) and δ_H 6.35 (1H, brs, 3-OH), respectively.

Table 1 also exhibits signals for hydrogen-bonded hydroxyl proton at δ_H 13.50 (1H,s,1-OH), three olefinic proton signals at δ_H 5.20 (1H, *t*, *J* =5.30 Hz), 5.24 (1H, *t, J* = 5.5 Hz), 5.30 (1H, *t , J* = 7.35 Hz); three methylene proton signals at δ_H 3.46 (2H, *d, J* = 7.35 Hz), 3.56 (2H, *d, J* = 7.35 Hz), 4.11 (2H, *d, J* = 6.70 Hz); and six methyl proton signals at δ_H 1.77 (3H, s, H-15), 1.85 (3H, s, H-16), 1.85 (3H,s, H-20),1.68 (3H,s, H-21), 1.89 (3H,s, H-25), 1.69 (3H, s, H-26) indicating three 3-methyl–2-enyl structure. Compound **2** contains two methoxyl groups at δ_H 3.69 (3H, s) and 3.79 (3H, s). The ^{13}C NMR signal assigned the oxygenated quaternary aromatic carbons 4a (δ_C 155.30); 5a (δ_C 152.73); 9a (δ_C 114.92), and substituted aromatic carbon C-11 abandon to the carbonyl carbon of depsidone. In the HMBC spectrum (Table 1), the hydrogen-bonded hydroxyl proton signal at δ_H 13.80 (H-1′) was correlated with the signal at δ_c 161.91 (C-1) and δ_C 108.57 (C-2) which showed that the hydroxyl group is located at C-1 position. Two methoxyl signals at δ_H 3.96 (3H, s) and δ_H 3.79 (3H, s) were correlated with the signal at δ_c 156.61 (C-7) and δ_c 147.96 (C-8), as well as C-8 (δ_c 147.96). It significantly demonstrated that H-27 attached to C-7 and H-28 attached to C-8, which indicates that



a b

Fig. 2. HMBC (a) and COSY (b) correlations of **2**.

methoxyls are located at C-2 and C3 positions of **2** (Fig. 2). The ^{13}C NMR signals at δ_C 182.87 (C=O) and strong absorption at ν_{max} 1644 cm^{-1} in the IR spectrum indicated a characteristic of lactone carbonyl and showed that compound **2** is a depsidone.[15] These data allowed us to assign the structure of **2** as 1,3-dihydroxy-7,8-dimethoxy-2,6,9tris(3-methylbut-2-enyl)-11*H*-dibenzo[*b,e*][1-4] dioxepin -11-one, which was given as the name pervidepsidone.

Previous studies reported some depsidones have been isolated form Garcinia genus, namely schomburgdepsidone B from *Garcinia schomburgkiana*[15] and garcidepsidone B from *G. parvifolia*.[16] The NMR spectral data of **2** were similar to those schomburgdepsidone B isolated from *Garcinia schomburgkiana,*[15] except for the replacement of hydroxyl on C-7 [δ_H 3.96 (3H, s); δ_C 60.99] and C-8 [δ_H 3.79 (3H, s); δ_C 60.81] of ring B to methoxyl, as well as substitution of methoxyl on C-3 of ring A to hydroxyl. Compared to study conducted by Rukachaisirikul (2008),[16] parvidepsidone showed different structure in ring A, in which parvidepsidone has one isophrene in C-2 while the previously reported garcidepsidone B has two isophrene in the same position, suggesting this compound is a new depsidone isolated from *G. parvifolia* Miq.

Among isolated compounds from this current study, stigmasterol and rubraxanthone have been reported to possess several pharmacological activities including anti-inflamatory,[17,18] antioxidant,[19,20] and anticarcinogenic.[21,22] Altogether, this present study reported that three compounds have been successfully isolated from the bark of *G. parvifolia* Mig. Based on spectral data, the structures of isolated compounds were determined as stigmasterol (**1**), parvidepsidone (**2**) and rubraxhantone (**3**). Out of those three, compound **2** (parvidepsidone) is considered as a novel depsidone from the barks of *G. parvifolia* Miq. However, further studies are necessary to identify the potential of these compounds, particularly parvidepsidone, for bioactivity-related research materials.

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