Supporting Information

***Rec. Nat. Prod*. 9:2 (2015) 243-246**

Potent Antiplasmodial Alkaloids and Flavonoids from *Dasymaschalon acuminatum*

Ratchanaporn Chokchaisiri[1*], Waraluck Chaichompoo[2], Rattana Chalermglin[3], and Apichart Suksamrarn[2]

[1]Department of Chemistry, School of Science, University of Phayao, Maeka, Muang, Phayao 56000, Thailand

[2]Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Ramkhamhaeng University, Bangkok 10240, Thailand

[3]Department of Chemistry, Faculty of Science and Technology, and Alternative Medical College, Chandrakasem Rajabhat University, Bangkok 10900, Thailand

Table of Contents **Page**

*Corresponding author: E- Mail: ratchanaporn.ch@up.ac.th; pam_2022@hotmail.com (R. Chokchaisiri)

Table of Contents **Page**

Extraction and Isolation of the air-dried leaves of *D. acuminatum*

The air-dried leaves of *D. acuminatum* (1.0 kg) were pulverized and extracted successively with *n*-hexane, EtOAc and MeOH at room temperature. The filtered solution of each extraction was evaporated to dryness under reduced pressure at temperature 40-45 ^{o}C to give the hexane extract (129.7 g), the EtOAc extract (15.74 g) and the MeOH extract (30.6 g).

EtOAc extract

The EtOAc extract (15.0 g) was fractionated by column chromatography (Merck silica gel 60, 0.063-0.200 mm, 520 g), using a gradient solvent system of *n*-hexane, *n*-hexane-EtOAc and EtOAc with increasing amounts of the more polar solvent. The eluates were examined by TLC and 7 groups of eluting fractions were obtained.

Group 2 (247.6 mg) was separated on Sephadex LH-20 eluting with CH_2Cl_2-MeOH to afford 3,5,7-trimethoxyflavone (**6**) as pale yellow amorphous solid (131.1 mg).

Group 3 (806.0 mg) was separated by Sephadex LH-20 eluting with CH_2Cl_2-MeOH to give four fractions (fr.3.1-3.4). Fraction 3.2 (338.9 mg) was subjected to repeated column chromatography eluting under isocratic condition of CH_2Cl_2-MeOH (98:2) to yield 5,7-dimethoxy-3-hydroxyflavone (**5**) as white amorphous solid (273.5 mg). Fraction 3.3 (411.3 mg) was separated by column chromatography using by isocratic solvent system of *n*-hexane-EtOAc (80:20) to yield galangin 5-methyl ether (**4**) as pale yellow amorphous solid (68.0 mg).

Group 7 (1.84 g) was chromatographed and eluted under isocratic condition of *n*-hexane-EtOAc (80:20), followed by Sephadex LH-20 eluting with CH_2Cl_2-MeOH (20:80) to give three fractions (fr.7.1-7.3). Fraction 7.2 was chromatographed over silica gel and eluted under isocratic condition of CH_2Cl_2-MeOH (98:2) to afford 3 subfractions (fr.7.2.1- fr.7.2.3). Subfraction 7.2.2 (723.0 mg) was separated on Sephadex LH-20 eluting with CH_2Cl_2-MeOH (20:80) to yield dicentrinone (**2**) as pale yellow amorphous solid (7.1 mg).

MeOH extract

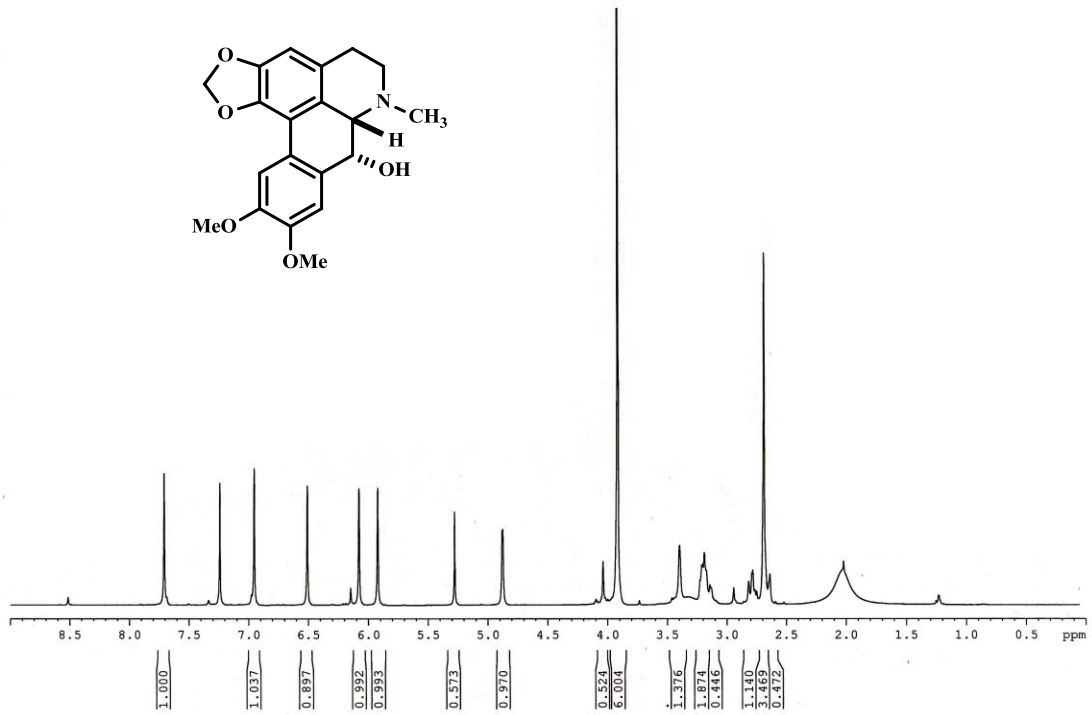
The MeOH extract (30.0 g) was fractionated by column chromatography (Merck silica gel 60, 0.063-0.200 mm, 520 g), using a gradient solvent system of *n*-hexane, *n*-hexane-EtOAc and EtOAc with increasing amounts of the more polar solvent. The eluates were examined by TLC and 6 groups of eluting fractions were obtained.

Group 3 (3.45 g) was separated on Sephadex LH-20 eluting with CH_2Cl_2-MeOH (20:80) to give three fractions (fr.3.1-3.3). Fraction 3.2 (2.54 mg) was subjected to repeated column chromatography eluting under isocratic condition of CH_2Cl_2-MeOH (97:3) to yield

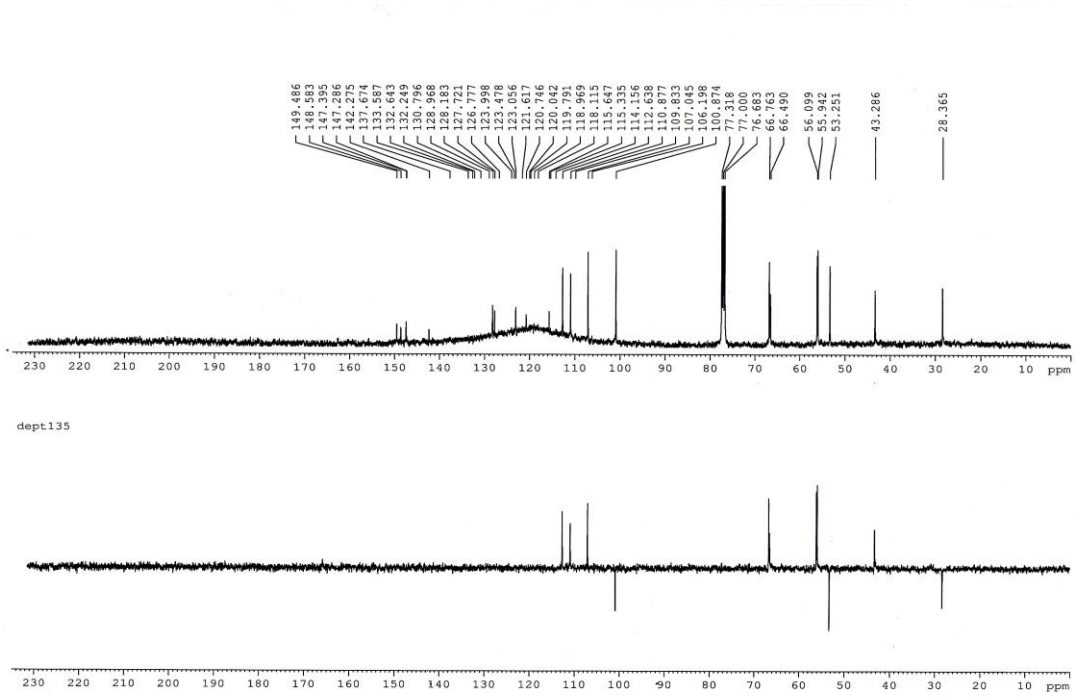
galangin 5-methyl ether (**4**) (321.4 mg) and 5,7-dimethoxy-3-hydroxyflavone (**5**) (1.35 g) similar to EtOAc extract.

Group 5 (10.3 g) was separated on Sephadex LH-20 eluting with CH_2Cl_2-MeOH (20:80) to give three subfractions (fr.5.1-5.3). Fraction 5.2 (2.73 g) was subjected to repeated column chromatography eluting under isocratic condition of CH_2Cl_2-MeOH (98:2) to give four subfractions (fr.5.2.1-5.2.4). Subfraction 5.2.2 (51.5 mg) was further purified by column chromatography over silica gel RP-18 with MeOH-H_2O (80:20) as eluting solvent to obtain 7-*epi*-duguetine (**1**) (46.8 mg). Subfraction 5.2.4 (1.00 g) was further purified by column chromatography over silica gel RP-18 with MeOH-H_2O (80:20) as eluting solvent to give quercetin 3,7-dimethyl ether 3′-*O*-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-glucopyranoside (**3**) as pale yellow amorphous solid (7.3 mg).

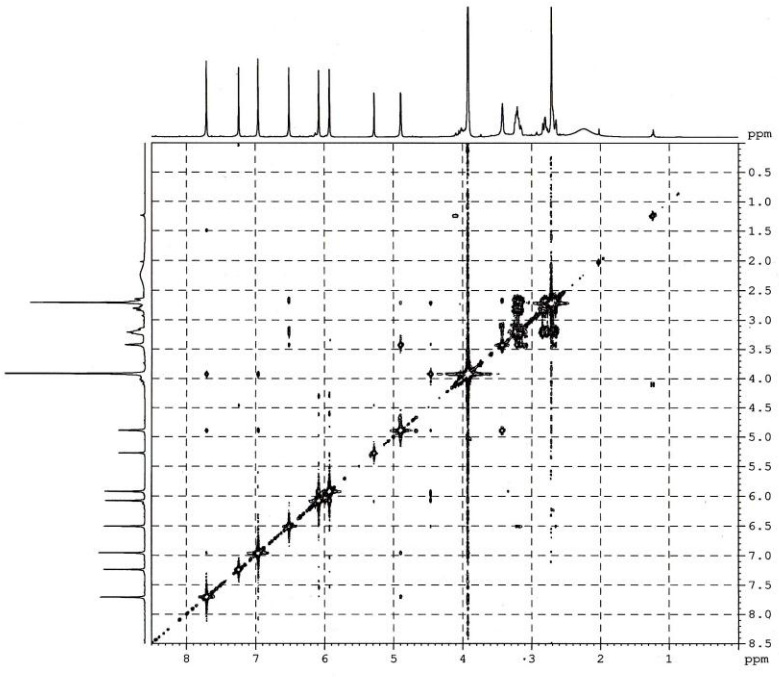
Compound 1: 7-epi-duguetine; Pale yellow amorphous solid; $[\alpha]^{32}_{D}$ –46.6˚ (*c* 0.59, $CHCl_3$), IR ν_{max} 3439, 1607, 1585, 1519, 1457, 1408, 1391, 1345, 1268, 1246, 1217, 1167, 1127, 1096, 1047, 1032, 969, 935 cm^{-1};HRESIMS *m/z*: 356.1447 $[M+H]^+$ (Calc. for $C_{20}H_{21}NO_5$, 356.1492).



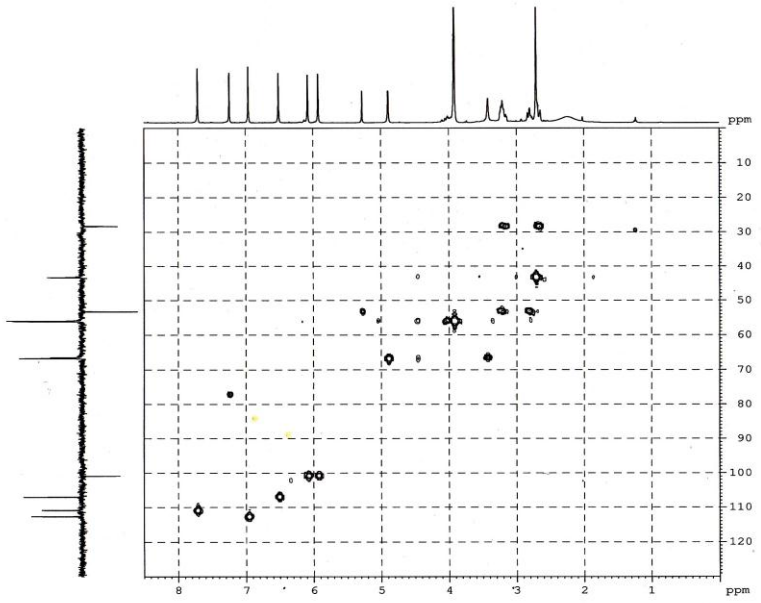
S1. ^{1}H-NMR spectrum of 7-*epi*-duguetine (**1**) in $CDCl_3$



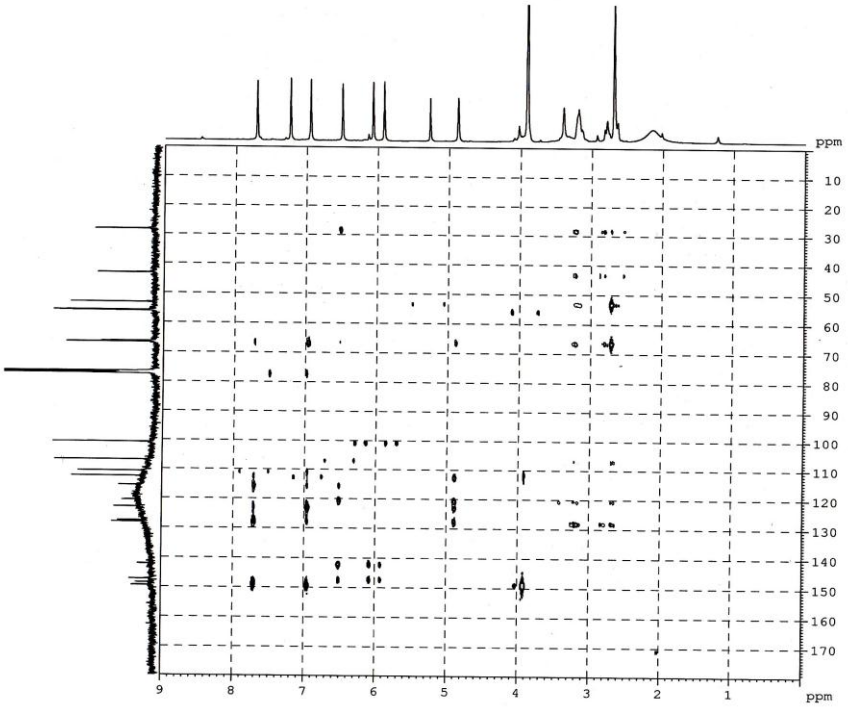
S2. ^{13}C-NMR and DEPT 135 spectra of 7-*epi*-duguetine (**1**) in $CDCl_3$



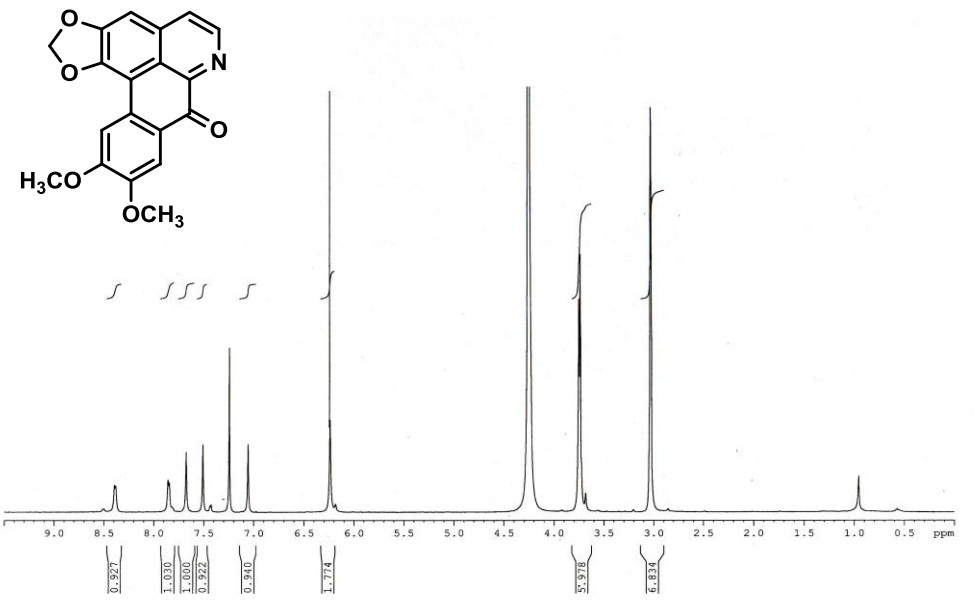
S3. COSY spectrum of 7-*epi*-duguetine (**1**) in $CDCl_3$



S4. HMQC spectrum of 7-*epi*-duguetine (**1**) in $CDCl_3$

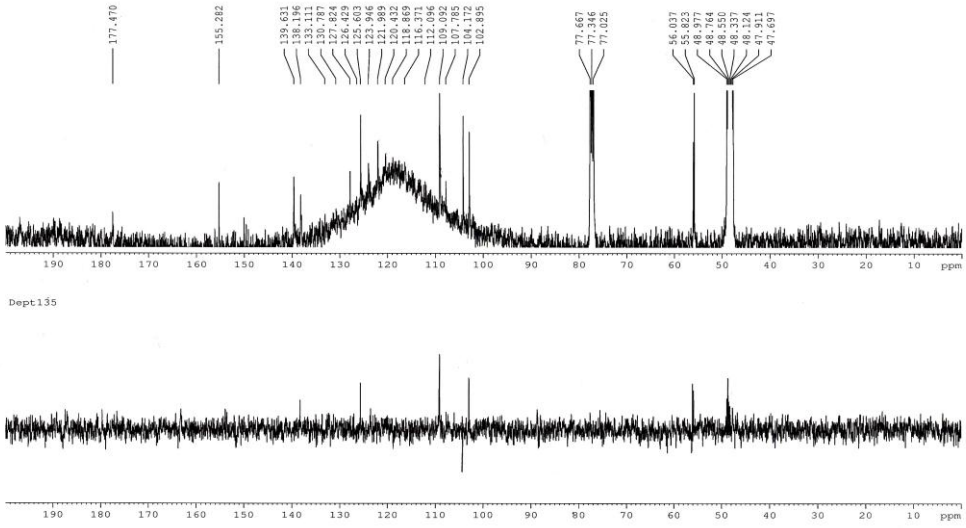


S5. HMBC spectrum of 7-*epi*-duguetine (**1**) in $CDCl_3$



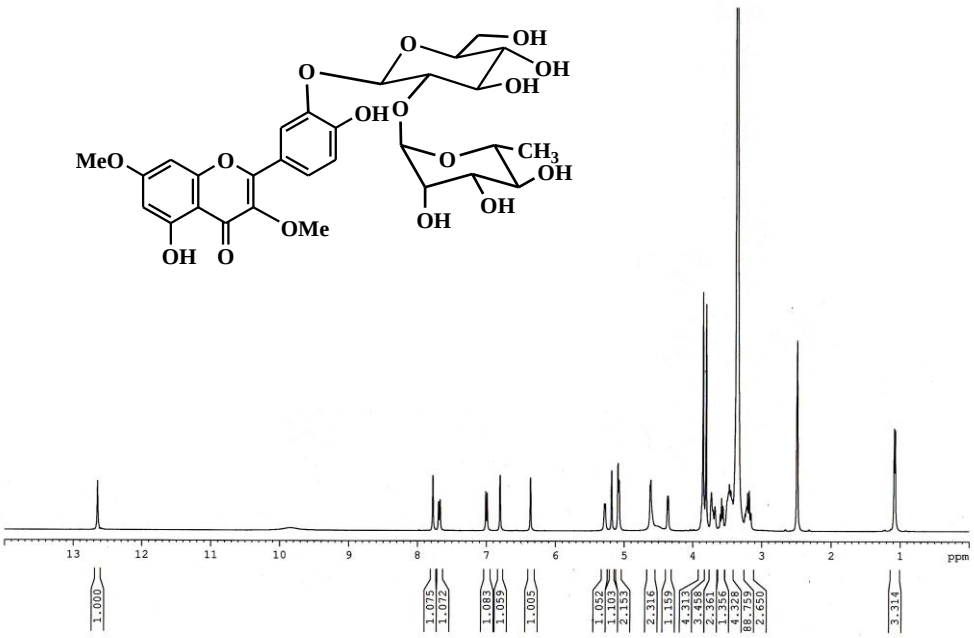
S6. ^{1}H-NMR spectrum of dicentrinone (**2**) in $CDCl_3$+8 drops CD_3OD

Dicentrinone (2): ^{1}H-NMR ($CDCl_3$+8 drops CD_3OD, 400 MHz), δ: 8.38 (1H, *d*, *J* = 4.8 Hz, H-5), 7.84 (1H, *d*, *J* = 4.8 Hz, H-4), 7.67 (1H, *s*, H-11), 7.50 (1H, *s*, H-8), 7.05 (1H, *s*, H-3), 6.23 (2H, *s*, O-CH_2-O), 3.75 (3H, *s*, 10-OCH_3), 3.73 (3H, *s*, 9-OCH_3).



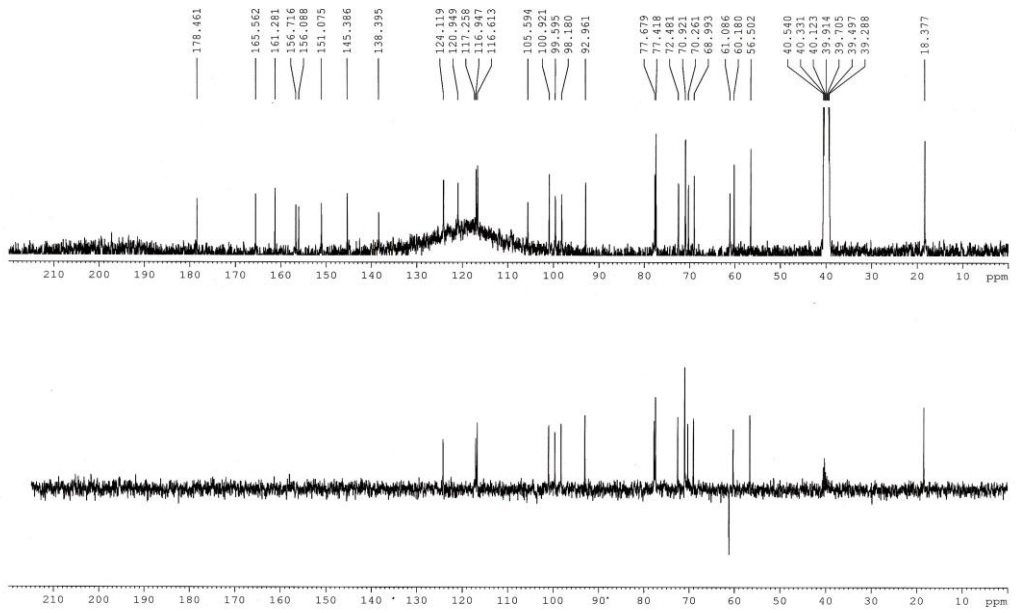
S7. ^{13}C-NMR and DEPT 135 spectra of dicentrinone (**2**) in $CDCl_3$+8 drops CD_3OD

Dicentrinone (2): ^{13}C-NMR ($CDCl_3$+8 drops CD_3OD, 100 MHz) δ 177.4 (C-7), 155.2 (C-10), 155.1 (C-1), 150.0 (C-6a), 149.5 (C-2), 149.1 (C-9), 139.6 (C-3a), 138.1 (C-5), 127.8 (C-11a), 125.6 (C-4), 123.9 (C-1a), 121.9 (C-1b), 109.0 (C-8), 109.0 (C-11), 107.7 (C-7a), 104.1 (O-CH_2-O), 102.8 (C-3), 56.0 (C-9OCH_3), 55.8 (C-10OCH_3).



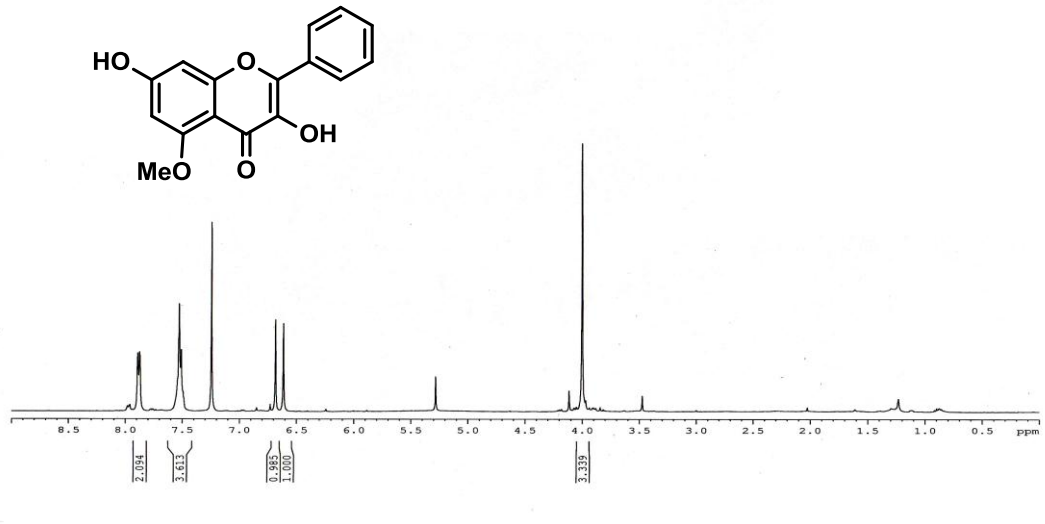
S8. [1]H-NMR spectrum of quercetin 3,7-dimethyl ether 3′-*O*-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-glucopyranoside (**3**) in DMSO-d_6

Quercetin 3,7-dimethyl ether 3'-O-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside (**3**): [1]H-NMR (DMSO-d_6, 400 MHz), δ: 12.6 (1H, *br s*, 5-OH), 7.77 (1H, *s*, H-2'), 7.68 (1H, *d*, *J* = 8.5, Hz, H-6'), 6.99 (1H, *d*, *J* = 8.5 Hz, H-5'), 6.80 (1H, *d*, *J* = 1.4 Hz, H-8), 6.36 (1H, *d*, *J* = 1.4 Hz, H-6), 3.85 (3H, *s*, 7-OCH_3), 3.81 (3H, *s*, 3-OCH_3), glucose unit; 5.08 (1H, *d*, *J* = 5.5 Hz, H-1"), 3.68 (1H, *br s*, H-6"b), 3.58 (1H, *t*, *J* = 8.0 Hz, H-5"), 3.50 (1H, *m*, H-6"a), 3.47 (1H, *m*, H-2"), 3.47 (1H, *m*,, H-3"), 3.22 (1H, *m*, H-4"), rhamnose unit; 5.18 (1H, *s*, H-1'"), 3.85 (1H, *s*, H-5'"), 3.73 (1H, *m*, H-2'"), 3.48 (1H, *m*,, H-3'"), 3.18 (1H, *m*, H-4'"), 1.08 (1H, *d*, *J* = 5.9 Hz, H-6'").



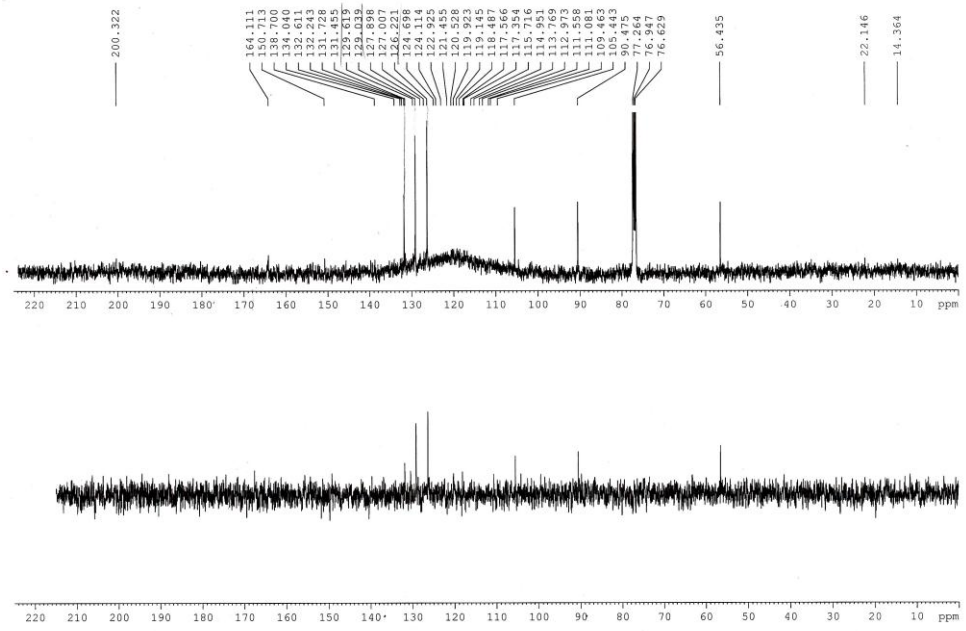
S9. ^{13}C-NMR and DEPT 135 spectra of quercetin 3,7-dimethyl ether 3′-*O*-*α*-L-rhamnopyranosyl-(1 → 2)-*β*-D-glucopyranoside (**3**) in DMSO-d_6

Quercetin 3,7-dimethyl ether 3′-O-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside (**3**): ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 178.4 (C-4), 165.5 (C-7), 161.2 (C-5), 156.7 (C-9),156.0 (C-2), 151.0 (C-4′), 145.3 (C-3′), 138.4 (C-3), 123.1 (C-6′), 120.9 (C-1′),116.9 (C-2′), 116.6 (C-5′), 105.5 (C-10), 98.9 (C-8), 98.1 (C-6), 60.1 (C-3OCH_3), 56.5 (C-7OCH_3), glucose unit; 99.6 (C-1″), 77.6 (C-5″), 77.4 (C-2″), 77.4 (C-3″), 77.2 (C-4″), 61.0 (C-6″), rhamnose unit; 100.92 (C-1‴), 72.4 (C-4‴), 70.9 (C-2‴), 70.9 (C-3‴), 68.9 (C-5‴), 18.3 (C-6‴).



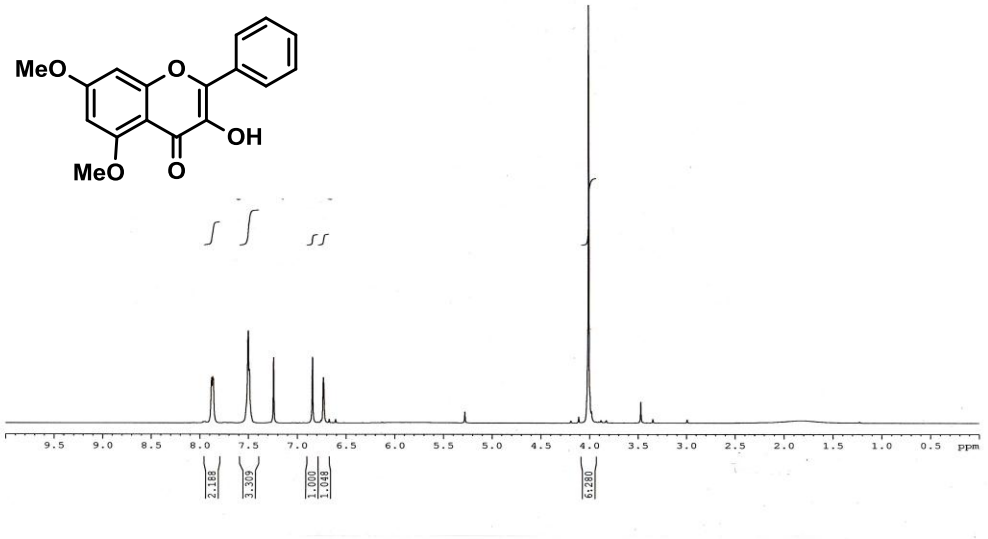
S10. ^{1}H-NMR spectrum of galangin 5-methyl ether (**4**) in $CDCl_3$

Galangin 5-methyl ether (4): ^{1}H-NMR ($CDCl_3$, 400 MHz), δ: 7.88 (2H, *d*, *J* = 6.3 Hz, H-2', 6'), 7.51 (3H, *m*, H-3', 4',5'), 6.72 (1H, *s*, H-8), 6.61 (1H, *s*, H-6), 3.96 (3H, *s*, 5-OCH_3).



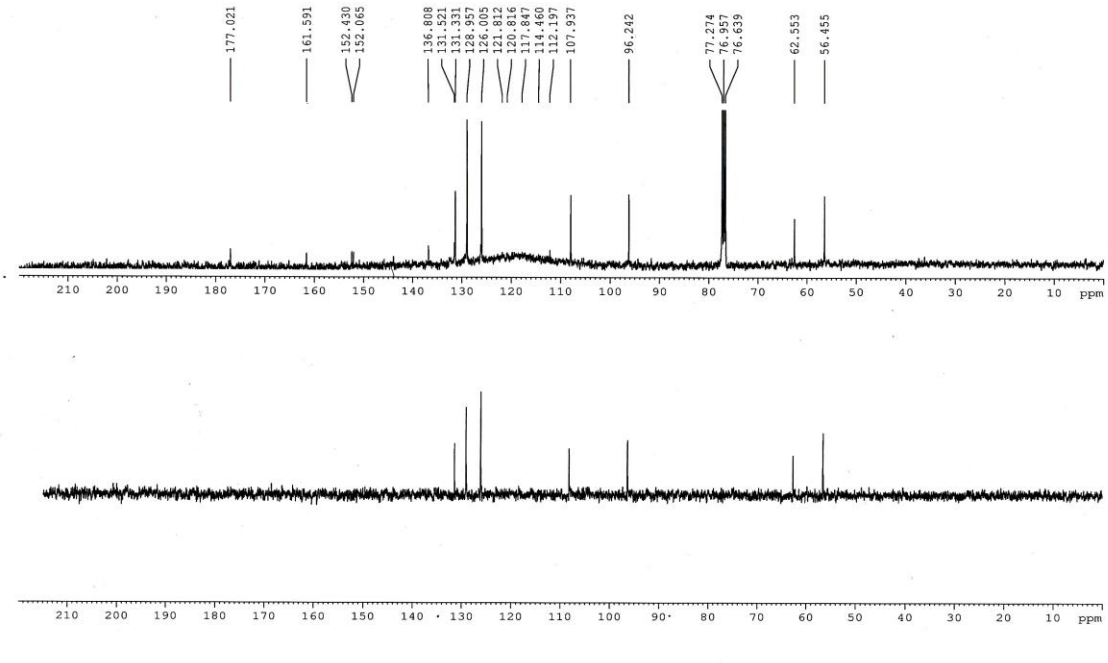
S11. ^{13}C-NMR and DEPT 135 spectra of galangin 5-methyl ether (**4**) in $CDCl_3$

Galangin 5-methyl ether (4): ^{13}C-NMR ($CDCl_3$, 100 MHz), δ: 183.0 (C-4), 168.0 (C-9), 164.1 (C-2), 153.1 (C-5), 150.7 (C-7), 136.8 (C-1'), 129.6 (C-4'), 129.0 (C-3',5'), 126.2 (C-2',6'), 106.5 (C-10), 105.4 (C-8), 90.4 (C-6), 56.4 (OCH3, C-5).



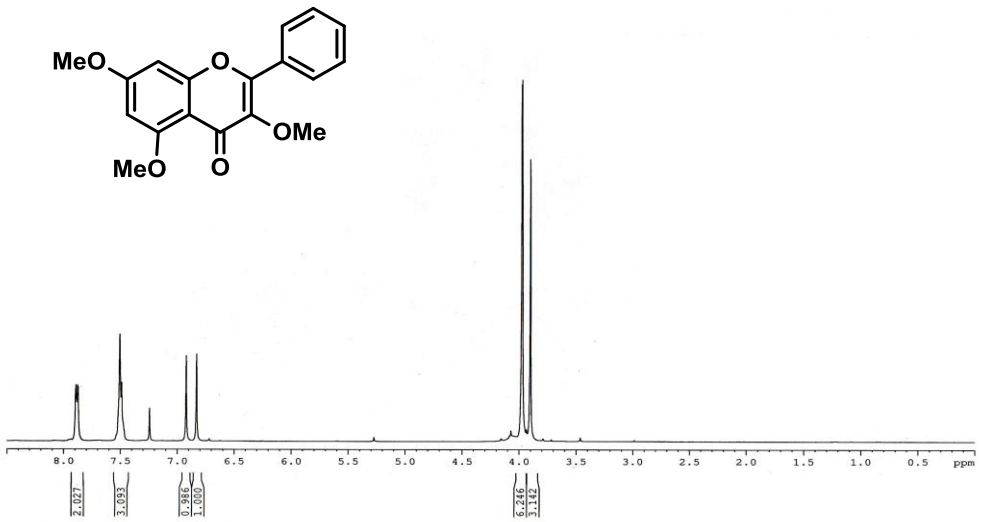
S12. ^{1}H-NMR spectrum of 5,7-dimethoxy-3-hydroxyflavone (**5**) in $CDCl_3$

5,7-Dimethoxy-3-hydroxyflavone (5): ^{1}H-NMR ($CDCl_3$, 400 MHz), δ: 7.86 (2H, *dd*, *J* = 7.5, 2.8 Hz, H-2', 6'), 7.49 (3H, *m*, H-3', 4',5'), 6.84 (1H, *s*, H-6), 6.73 (1H, *s*, H-8), 4.01 (3H, *s*, 7-OCH_3), 4.01 (3H, *s*, 5-OCH_3).



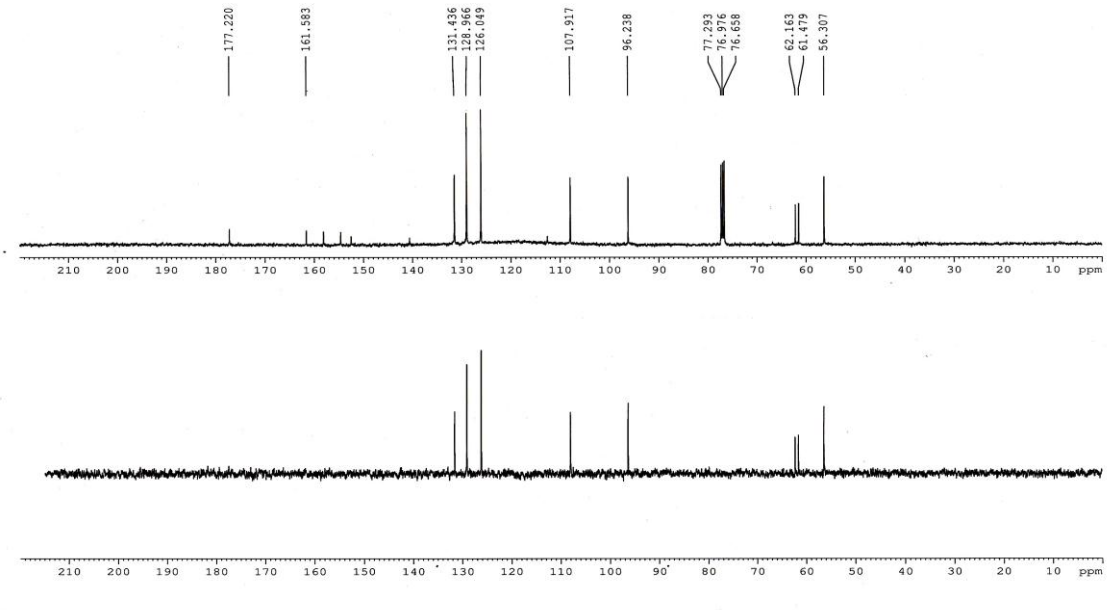
S13. ^{13}C-NMR and DEPT 135 spectra of 5,7-dimethoxy-3-hydroxyflavone (**5**) in $CDCl_3$

5,7-Dimethoxy-3-hydroxyflavone (5): ^{13}C-NMR ($CDCl_3$, 100 MHz), δ: 177.0 (C-4), 165.3 (C-9), 161.5 (C-2), 152.4 (C-5), 152.0 (C-7), 136.8 (C-1'), 131.3 (C-4'), 128.9 (C-3',5'), 126.0 (C-2',6'), 112.1 (C-10), 107.9 (C-8), 96.2 (C-6), 62.5 (OCH_3, C-5), 56.4 (OCH_3, C-7).



S14. ^{1}H-NMR spectrum of 3,5,7-trimethoxyflavone (**6**) in $CDCl_3$

3,5,7-Trimethoxyflavone (6): ^{1}H-NMR ($CDCl_3$, 400 MHz), δ: 7.87 (2H, *dd*, J = 7.7, 1.7 Hz, H-2', 6'), 7.49 (3H, *m*, H-3',4',5'), 6.91 (1H, *s*, H-6), 6.82 (1H, *s*, H-8), 3.97 (3H, *s*, 7-OCH_3), 3.97 (3H, *s*, 5-OCH_3), 3.90 (3H, *s*, 3-OCH_3).



S15. ^{13}C-NMR and DEPT 135 spectra of 3,5,7-trimethoxyflavone (**6**) in $CDCl_3$

3,5,7-Trimethoxyflavone (6): ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 177.2 (C-4), 161.5 (C-9), 158.2 (C-1'), 154.8 (C-7), 152.5 (C-2), 144.6 (C-5), 131.4 (C-4'), 128.9 (C-3',5'), 126.0 (C-2',6'), 112.9 (C-10), 109.9 (C-8), 96.2 (C-6), 62.1 (OCH_3, C-7), 61.4 (OCH_3, C-3), 56.3 (OCH_3, C-5).

SHORT REPORT

A C G publications

Rec. Nat. Prod. 9:2 (2015) 243-246

records of natural products

Potent Antiplasmodial Alkaloids and Flavonoids from *Dasymaschalon acuminatum*

Ratchanaporn Chokchaisiri[1*], Waraluck Chaichompoo[2], Rattana Chalermglin[3] and Apichart Suksamrarn[2]

[1]*Department of Chemistry, School of Science, University of Phayao, Maeka, Muang, Phayao 56000, Thailand*
[2]*Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Ramkhamhaeng University, Bangkok 10240, Thailand*
[3]*Department of Chemistry, Faculty of Science and Technology, and Alternative Medical College, Chandrakasem Rajabhat University, Bangkok 10900, Thailand*

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Abstract: A new aporphine alkaloid, 7-*epi*-duguetine (**1**) together with one known alkaloid, dicentrinone (**2**), and four known flavonoids, quercetin 3,7-dimethyl ether 3′-*O*-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-glucopyranoside (**3**), galangin 5-methyl ether (**4**), 5,7-dimethoxy-3-hydroxyflavone (**5**), and 3,5,7-trimethoxyflavone (**6**), were isolated from the leaves of *Dasymaschalon acuminatum*, a new plant species which has not been investigated phytochemically before. The structures of the isolated compounds were elucidated through extensive NMR spectroscopic analysis. All isolates were evaluated for antiplasmodial activity against *Plasmodium falciparum* strain K1 and 7-*epi*-duguetine was found to exhibit potent activity with an IC_{50} of 0.385 μg/ml.

Keywords: *Dasymaschalon acuminatum*; Annonaceae; alkaloid; flavonoid; antiplasmodial activity.

1. Plant Source

Dasymaschalon acuminatum Jing Wang & R.M.K. Saunders (Annonaceae) is known in Thai as "Bu-rong Dok Laem" [1]. The leaves of this plant species were collected from Khao Yai National Park, Nakorn Ratchasima province, Thailand in August 2010 and the plant species was identified by Dr. Piya Chalermglin, Thailand Institute of Scientific and Technological Research, Bangkok, Thailand. The voucher specimen (C. Phengklai 3272) is deposited at The Forest Herbarium, Department of National Parks, Wildlife and Plant Conservation, Chatuchak, Bangkok, Thailand.

2. Previous Studies

Dasymaschalon is a genus which includes over 30 species distributed in South-East Asia, particularly in Thailand and Malaysia. In Thailand, 12 species have been reported; *D. acuminatum, D. angustifolium, D. dasymaschalum, D. echinatum, D. filipes, D. glaucum, D. grandiflorum, D. lomentaceum, D. macrocalyx, D. obtusipetalum, D. sootepense,* and *D. wallichii* [1]. The phytochemical investigations of various *Dasymaschalon* species revealed the presence of alkaloids [2], acetogenins [3], xanthones [4], and flavonol glycosides [5]. Some of the compounds have shown promising

* Corresponding author: E- Mail: ratchanaporn.ch@up.ac.th; pam_2022@hotmail.com (R. Chokchaisiri)

cytotoxic activity [3,4]. Since *D. acuminatum* is recognized as a new species of *Dasymaschalon* [1], no phytochemical investigation of this plant species has been reported.

3. Present Study

The air-dried leaves of *D. acuminatum* (1.0 kg) were pulverized and extracted successively with *n*-hexane, EtOAc and MeOH at room temperature. The filtered solution of each extract was evaporated to dryness under reduced pressure at temperature 40-45 ^{o}C to give the hexane extract (129.7 g), the EtOAc extract (15.74 g) and the MeOH extract (30.6 g). The isolation details are shown in the supplementary material. Each of the extracts was purified by chromatographic techniques to yield a new aporphine alkaloid, 7-*epi*-duguetine (**1**), together with one known alkaloid, dicentrinone (**2**) [6], and four known flavonoids, quercetin 3,7-dimethyl ether 3′-*O*-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-glucopyranoside (**3**) [5], galangin 5-methyl ether (3,7-dihydroxy-5-methoxyflavone) (**4**) [7], 5,7-dimethoxy-3-hydroxyflavone (**5**) [8], and 3,5,7-trimethoxyflavone (**6**) [9] (Figure 1). The structure of the new compound was elucidated on the basis of spectroscopic analysis, and those of known compounds were identified by comparison of the spectroscopic data with those reported in the literature.

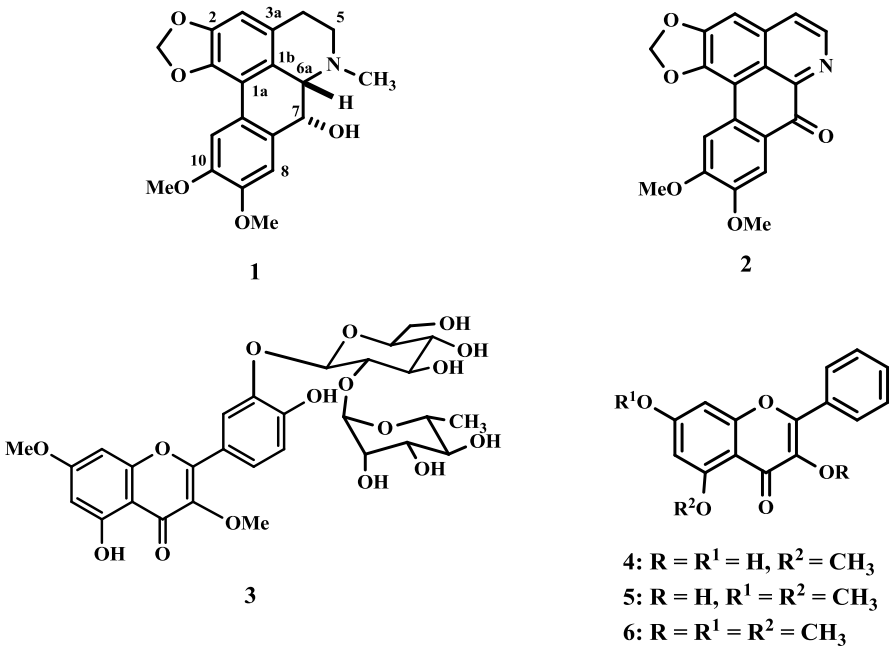

Figure 1. Structure of alkaloids (**1**-**2**) and flavonoids (**3**-**6**) isolated from *D. acuminatum.*

Compound **1** was obtained as a yellow amorphous solid. The HRESIMS showed a pseudo-molecular ion $[M + H]^+$ at *m/z* 356.1447 in accordance with the molecular formula $C_{20}H_{21}NO_5$. The ^{1}H-NMR spectra showed a singlet corresponding to the protons of two OCH_3 groups at δ_H 3.91, which could be placed at C-9 and C-10 as evident from the HMBC correlations between 9-OCH_3 protons and C-9 (δ_C 149.5) and between 10-OCH_3 and C-10 (δ_C 148.9). Two singlets of the methylenedioxy protons were observed at δ_H 5.93 and 6.09. Three singlets at δ_H 6.51, 6.95 and 7.70 attributable to H-3, H-8 and H-11 respectively, confirmed the substitution patterns of the aromatic rings as shown. The hydroxyl proton and the N-linked methyl group appeared as singlet signals at δ_H 5.01 and 2.69. Compound **1** should therefore be an aporphine alkaloid having a 1,2-methylenedioxy and two methoxy groups. A carbinolic signal at δ_H 4.87 (d, J = 2.1 Hz) could be placed at C-7 from the ^{1}H-^{1}H COSY correlations between H-7 and H-6a (Figure 2), and the HMBC correlations between H-7 and C-1b, C-6a, C-7a C-8 and C-11a (Table 1). The absolute configuration of the chiral center C-6a of **1** was established as *R* as determined from the circular dichroism (CD) curve, which showed a negative Cotton effect at 242 nm [10]. The small $J_{6a,7}$ of 2.1 Hz of **1** indicated the *cis*-relationship of H-6a and

H-7, which was characteristically different from that of the *trans* (J = 12 Hz) C-7 isomeric form [11]. This was further confirmed by the NOE enhancement of H-6a (δ_H 3.39) and H-7 (δ_H 4.87). The absolute configuration at C-7 was therefore established as *R*. These data, together with a comparison with those of (–)-duguetine, established the structure of compound **1** as the C-7 epimer of (–)-duguetine. Thus, compound **1** was named 7-*epi*-duguetine.

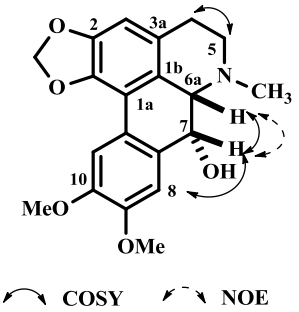

Figure 2. The COSY and NOE correlations of compound **1**.

Table 1. ^{1}H- and ^{13}C-NMR data of compound 1 (at 400 and 100 MHz, respectively, in $CDCl_3$)

Position	δ_H ppm, J (Hz)	δ_C, ppm	HMBC
1	-	142.7	-
1a	-	115.8	-
1b	-	120.7	-
2	-	147.3	-
3	6.51 (s)	107.0	C-1; C-1b; C-2; C-4
3a	-	128.1	-
4	3.14∗, 2.66∗	26.3	C-1b; C-3a; C-5
5	3.21∗, 2.78 (dd, 10.4, 3.2)	53.2	C-3a; C-4; C-6a; N-CH_3
6a	3.39 (br s)	66.4	C-1b; N-CH_3
7	4.87 (d, 2.1)	65.2	C-1b; C-6a; C-7a; C-8; C-11a
7a	-	127.7	-
8	6.95 (s)	112.6	C-7; C-7a; 9-OCH_3
9	-	149.5	-
10	-	148.9	-
11	7.70 (s)	110.8	C-1a; C-7a; C-11a; 10-OCH_3
11a	-	123.0	-
N-CH_3	2.69 (s)	43.2	C-5; C-6a
O-CH_2-O	6.09 (s), 5.93 (s)	100.8	C-1; C-2
9-OCH_3	3.91 (s)	56.0	C-9
10-OCH_3	3.91 (s)	55.9	C-10

∗ partially overlapping signal

The antiplasmodial activity of all isolated compounds was determined *in vitro* against the chloroquine-resistant K1 strain of *Plasmodium falciparum* by using the microculture radioisotope method [12,13]. Compound **1** was the most active compound with an IC_{50} value of 0.385 μg/ml, while compounds **2**, **4** and **5** showed moderate to weak activity with respective IC_{50} values of 1.23, 5.07 and 3.12 μg/ml, whereas compounds **3** and **6** were inactive (IC_{50} > 10 μg/ml). The IC_{50} value of the standard drug mefloquine was 0.011 μg/ml.

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/RNP

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