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Macagigantin, a farnesylated flavonol from *Macaranga gigantea*

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A new farnesylated flavonol derivative, macagigantin (**1**), together with two known flavonoids, glyasperin A (**2**) and apigenin (**3**), had been isolated from the acetone extract of the leaves of *Macaranga gigantea*. The structure of the new compound was elucidated as 6-farnesylokaempferol based on its spectroscopic data, including UV, IR, 1D and 2D NMR, and HR-EI-MS spectra. Compounds **1–3** were evaluated for their cytotoxic properties against P-388 cells, their IC₅₀ values being 11.3, 6.0, and 5.1 μM, respectively.

Keywords: macagigantin; farnesylated flavonol; *Macaranga gigantea*; Euphorbiaceae; cytotoxicity; P-388 cells

1. Introduction

The genus *Macaranga* (Euphorbiaceae) contains about 250 species distributed very widely from Africa and Madagascar in the west to tropical Asia, North Australia, and Pacific Islands in the east [1]. This genus has been shown to produce a number of phenolic compounds, particularly flavonoids and stilbenoids [2]. Recently, we have reported the first dihydrochalcone derivatives, along with flavanones, from an endemic *Macaranga* species in Indonesia, *Macaranga trichocarpa* [3]. In continuation of our phytochemical work on Indonesian tropical plants aiming to find new cytotoxic compounds [4–9], we had examined another *Macaranga* species, *Macaranga gigantea* (Reichb.f. & Zoll.) Müll. Arg. In this paper, we report the isolation of a farnesylated flavonol, 6-farnesylokaempferol (**1**), together with two

known compounds **2** and **3** (Figure 1), from the acetone extract of the title plant leaves. The cytotoxic properties of compounds **1–3** against murine leukemia P-388 cells are also briefly described.

2. Results and discussion

Compound **1** was isolated as a yellow solid and the molecular formula C₃₀H₃₄O₆ was deduced from its HR-EI-MS data. The UV spectrum of **1** exhibited maxima typical for a flavonol structure (λ_{max} 271, 348, and 283 nm), and showed bathochromic shifts on addition of AlCl₃ and NaOAc [10]. The IR spectrum indicated absorptions for hydroxyl (3419 cm⁻¹), conjugated carbonyl (1649 cm⁻¹), and aromatic (1608 and 1560 cm⁻¹) groups. In the ¹³C NMR spectrum (APT experiment; Table 1), 28 carbon signals representing 30 carbon atoms were observed. Two of them,

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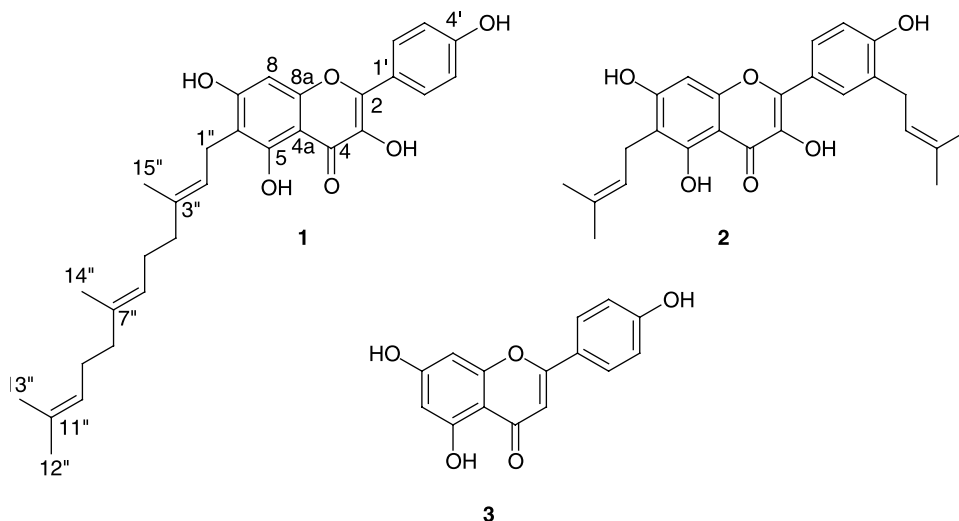


Figure 1. Structures of flavonoids 1–3.

namely the signals at δ_C 136.5 and 176.5, are characteristic for C-3 and C-4 of a flavonol structure [11,12]. These spectroscopic data, therefore, suggested that **1** is a flavonol containing a C-15 side chain. Moreover, the presence of other five oxyaryl signals (δ_C 146.6, 155.6, 158.1, 160.0, and 162.6) indicated that the flavonol is a derivative of kaempferol.

The side chain was deduced to be a farnesyl group from the observation in the ^1H NMR spectrum (Table 1) of four methyl singlets at δ_H 1.51, 1.54, 1.57, and 1.79, five methylene signals at δ_H 1.8–3.5, and three methine vinyl signals of three substituted alkenes at δ_H 5.00, 5.06, and 5.29. The presence of the proton signals of a pair of doublets ($J = 9.0$ Hz) in the aromatic region at δ_H 7.00 and 8.12 (each 2H), assignable to the signals of a *p*-hydroxyphenyl group, and a singlet at δ_H 6.59, suggested that the farnesyl group is either at C-6 or C-8 of the kaempferol structure. The presence of long-range correlations in the HMBC spectrum of **1** between the proton signal of a chelated —OH group at δ_H 12.41 and three quaternary carbon signals at δ_C 104.0 (C-4), 158.1 (C-5), and 111.7 (C-6) unambiguously placed the farnesyl group at C-6.

Therefore, compound **1**, trivially named macagigantin, was elucidated as 6-farnesylkaempferol or 6-[(2*E*,6*E*)-3'',7'',11''-trimethyldodeca-2'',6'',10''-trienyl]-kaempferol. Other HMBC correlations consistent with structure **1** are shown in Table 1. Further support for structure **1** was also obtained from the comparison of the NMR spectral data with those reported for 6-geranylkaempferol (macarangin) [11,12]. To our knowledge, compound **1** was the first example of flavonoid in the genus *Macaranga* with a farnesyl side chain.

On cytotoxic evaluation against P-388 cells, compounds **1–3** exhibited IC_{50} values of 11.3 ± 0.4 , 6.0 ± 0.9 , and 5.1 ± 0.7 μM , respectively (artnonin E as a positive control, IC_{50} 1.38 ± 0.2). These cytotoxic data suggested that the presence of a terpenoid (farnesyl) substituent at C-6 (ring A) of the kaempferol structure reduces cytotoxic properties, while a similar substituent (isoprenyl) in the ring B enhances cytotoxicity.

3. Experimental

3.1 General experimental procedures

UV and IR spectra were measured with a Varian 100 Conc and an FT-IR Spectrum

Table 1. The NMR spectral data (*d*₆-acetone) of compound 1.

No.	δ_{H} (multiplicity, <i>J</i> in Hz)	δ_{C}	HMBC (H \leftrightarrow C)
2	–	146.6	–
3	–	136.5	–
4	–	176.5	–
4a	–	104.0	–
5	–	158.1	–
6	–	111.7	–
7	–	162.6	–
8	6.59 (s)	93.8	C-4, C-4a, C-6, C-7, C-8a
8a	–	155.6	–
1'	–	123.4	–
2'/6'	8.12 (d, 9.0)	130.3	C-2, C-4', C-6'/2'
3'/5'	7.00 (d, 9.0)	116.2	C-4', C-1', C-5'/3'
4'	–	160.0	–
1''	3.37 (d, 6.7)	21.9	C-5, C-6, C-7, C-2'', C-3''
2''	5.29 (tm, 6.7)	123.2	C-1'', C-4'', C-15''
3''	–	135.1	–
4''	1.97 (t, 7.3)	40.4	C-2'', C-5'', C-3'', C-6'', C-15''
5''	2.06 (br q, 7.3)	27.0	C-4'', C-6'', C-7''
6''	5.06 (br t, 7.3)	124.8	C-5'', C-8'', C-14''
7''	–	135.4	–
8''	1.85 (br t, 7.3)	40.4	C-6'', C-7'', C-9'', C-10'', C-14''
9''	1.93 (br q, 7.3)	27.3	C-8'', C-10'', C-11''
10''	5.00 (br t, 7.3)	125.0	C-9'', C-12'', C-13''
11''	–	131.5	–
12''	1.57 (br s)	25.8	C-10'', C-11'', C-13''
13''	1.51 (br s)	17.6	C-10'', C-11'', C-12''
14''	1.54 (br s)	16.2 ^a	C-6'', C-7'', C-8''
15''	1.79 (br s)	16.1 ^a	C-2'', C-3'', C-4''
5-OH	12.41 (s)	–	C-4a, C-5, C-6

^aAssignments could be interchanged.

One Perkin-Elmer instrument, respectively. ¹H and ¹³C NMR spectra were recorded with a JEOL ECA500 spectrometer operating at 500 (¹H) and 125 (¹³C) MHz, using residual and deuterated solvent peaks (δ_{H} 2.04 and δ_{C} 29.8, respectively) as reference standards. Mass spectra were obtained with a VG Autospec mass spectrometer (EI mode). Vacuum liquid chromatography (VLC) and radial chromatography were carried out using Si gel 60 G (article no. 1.07731.1000, Merck KgaA, 64271 Darmstadt, Germany) and Si gel 60 PF₂₅₄ (article no. 1.07749.1000, Merck KgaA, 64271), respectively, and for TLC analysis, precoated Si gel 60 F₂₅₄ plates (article no. 1.05554.0001, Merck KgaA, 64271)

were used. Solvents used for extraction and separation were of technical grades that were distilled before use.

3.2 Plant material

The leaves of *M. gigantea* were collected in November 2007 from Lungkut Layang Village, District Kapuas, Kalimantan, Indonesia. The specimen was identified by Mr Ismail, Herbarium Bogoriense, Center of Biological Research and Development, National Institute of Science, Bogor, Indonesia, and the voucher specimen has been deposited at the herbarium.

3.3 Extraction and isolation

The dried and powdered leaves of *M. gigantea* (1.2 kg) were macerated in

acetone at room temperature (3×, 7.5 liters), and the acetone extract was evaporated under reduced pressure to give a crude acetone extract (50 g). The extract was fractionated by VLC on silica gel eluted with *n*-hexane–EtOAc mixtures [17:3 (4×) and 4:1 (4×)] to give five major fractions A–E. On TLC analysis, fraction D (1 g) showed two major spots (R_f 0.71 and 0.43, eluent CHCl_3 –EtOAc = 9:1) and on purification of this fraction using centrifugal planar chromatography eluted with *n*-hexane– CHCl_3 (7:3 → 1:9), CHCl_3 , and CHCl_3 –EtOAc (9:1) afforded macagigantin (**1**) (23 mg) and glyasperin A (**2**) (64 mg) [13]. The same procedure was applied to fraction E (330 mg) to give apigenin (**3**) (25 mg) [14].

3.3.1 Macagigantin (**1**)

A yellow solid. UV (MeOH) λ_{\max} (log ϵ): 204 (4.58), 271 (4.20), 333 (4.13), 368 (4.18) nm, (MeOH+NaOH) 210 (4.90), 240 (sh, 4.32), 279 (4.22), 322 (4.09), 417 (4.27) nm, (MeOH+ AlCl_3) 203 (4.59), 273 (4.27), 347 (3.85), 431 (4.25) nm, (MeOH+ AlCl_3/HCl) 203 (4.58), 272 (4.26), 348 (3.86), 431 (4.24) nm; (MeOH+NaOAc) 203 (4.85), 272 (4.21), 333 (4.07), 368 (4.06) nm; IR (KBr) ν_{\max} : 3419 (OH), 2922, 2852 (CH-alkyl), 1649 (conj. C=O), 1608, 1560 (C=C aromatic) cm^{-1} ; ^1H NMR (500 MHz) spectral data, see Table 1; ^{13}C NMR (125 MHz) spectral data, see Table 1; HR-EI-MS m/z : 490.2357 [$\text{M}]^+$ (calcd for $\text{C}_{30}\text{H}_{34}\text{O}_6$, 490.2355); EI-MS m/z (% rel.): 490 (17), 421 (24), 353 (56), 337 (15), 311 (12), 299 (100), 121 (10), 69 (25).

3.4 Cytotoxic evaluation

Cytotoxic properties of the isolated compounds **1–3** against murine leukemia P-388 cells were evaluated according to the method of MTT assay as described previously [15].

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