Fitoterapia 126 (2018) 74–77

Contents lists available at ScienceDirect

Fitoterapia

journal homepage: www.elsevier.com/locate/fitote

Flavonoid and stilbene derivatives from *Macaranga trichocarpa*

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ARTICLE INFO

Keywords:
Cytotoxicity
Euphorbiaceae
Macaranga trichocarpa
Macatrichocarpin *E*-H
4′-*O*-Methylmacagigantin
Flavonoid
Stilbene

ABSTRACT

A new farnesylated flavonol (4′-*O*-methylmacagigantin) and a new geranylated stilbene (macatrichocarpin H), together with eight known phenolic compounds, have been isolated from the leaves of *Macaranga trichocarpa*. Structures of these compounds were determined based on NMR and mass spectrroscopic data. Cytotoxic properties of the isolated compounds were tested against P-388 cells showing that mactrichocarpin G was the most active compound with IC_{50} was 3.5 μM.

1. Introduction

Macaranga (Euphorbiaceae) is the genus of plants inhabitated mostly in the tropical regions, including in the Indonesian archipelago [1]. The plants have been known to produce a variety of terpenylated flavonoids and stilbenes [2]. One of the species, namely *Macaranga trichocarpa* (Zoll.) Mull.Arg., is widely distributed in the western part of Indonesia, particularly in Sumatera and Kalimantan islands [3]. This plant is considered as a pioneer species for forest disturbances and is common to be found in a secondary forest [4]. Report on its medicinal use is a rather scarce, however, the people of Vietnam has used the decoction of the leaves to improve and maintain health [4]. Previous chemical investigation of the plant leaves collected from Kalimantan island has revealed a number of prenylated dihydrochalcone and flavanone derivatives [5,6]. Some of them were shown to have significant antibacterial properties [6]. In this paper we report the isolation of phenolic constituents from the leaves of this plant collected from Sumatera island. In addition to the previously isolated compounds, namely macatrichocarpins A-B (**1–2**), we succeded to isolate one new farnesylated flavonol, 4′-*O*-methylmacagigantin (**4**), and one new geranylated stilbene, macatrichocarpins H (**7**), together with other known stilbenes (**5** and **6**) and flavonoids (**3**, **8–10**) (Fig. 1). Structure elucidation of these new compounds will be the subject of this paper. In addition, preliminary cytotoxicity test of the isolated compounds against murine leukemia P-388 cells will also be described.

2. Experimental

2.1. General experimental procedure

^{1}H and ^{13}C NMR spectra were recorded with a JEOL ECA500 spectrometer operating at 500 (^{1}H) and 125 (^{13}C) MHz, using residual and deuterated solvent peaks (δ_H 7.26 and δ_C 77.0 for $CDCl_3$; δ_H 2.04 and δ_C 29.8 for acetone-d_6) as reference standards. High-resolution mass spectra were obtained with an ESI-TOF Waters LCT Premier XE mass spectrometer with either positive or negative mode.Vacuum liquid chromatography (VLC) and centrifugal planar (CPC) chromatography were carried out using Si gel 60 G (art. no. 1.07731.1000, Merck KgaA, 64,271 Darmstadt, Germany) and Si gel 60 PF_{254} (art. no. 1.07749.1000, Merck KgaA, 64,271 Darmstadt, Germany), respectively, and, for TLC analysis, precoated Si gel 60 F_{254} plates (art. no. 1.05554.0001, Merck KgaA, 64,271 Darmstadt, Germany) were used. Solvents used for extraction and separation were technical grades that were distilled before used.

2.2. Plant material

Samples of the leaves of *M. trichocarpa* were collected from Sungai Lilin District, South Sumatera, Indonesia, in December 2009. The specimen was identitified at the Herbarium Bogoriense, Center of Biological Research and Development, National Institute of Science,

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http://dx.doi.org/10.1016/j.fitote.2017.10.001
Received 3 August 2017; Received in revised form 27 September 2017; Accepted 1 October 2017
Available online 03 October 2017
0367-326X/

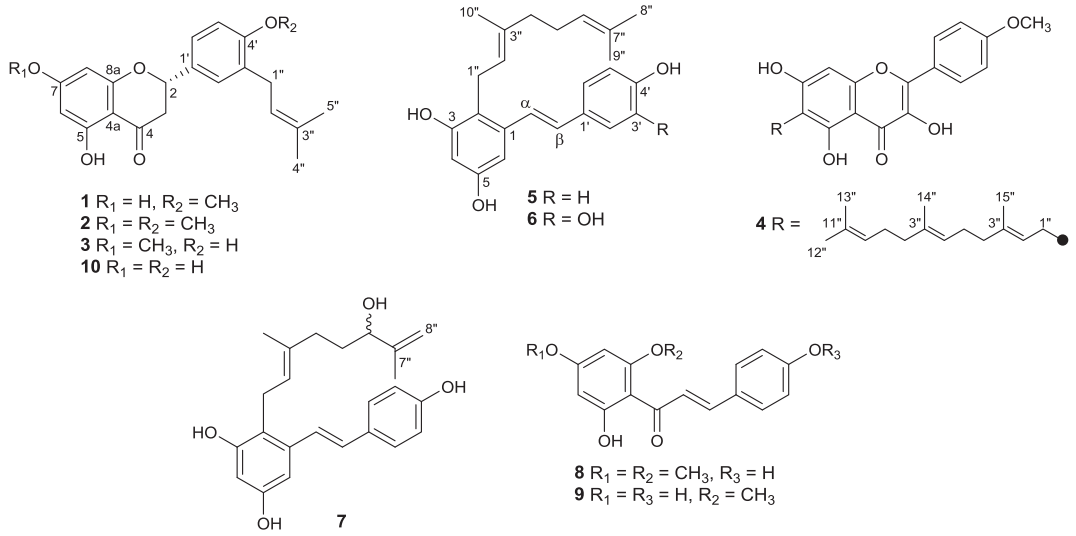

Fig. 1. Flavonoid and stilbene derivatives isolated from *M. trichocarpa*.

Bogor, Indonesia. The specimen (collection number HBG-13587), was deposited at herbarium Bandungense, School of Life Science and Technology, Institut Teknologi Bandung, Indonesia.

2.3. Extraction and isolation

The dried and powdered leaves of *M. trichocarpa* (650 g) was macerated with MeOH at room temperature (2 × 24 h) to give a dark MeOH extract (70 g) after solvent evaporation. The MeOH extract was dissolved MeOH-water (9:1) and was partitioned into *n*-hexane (48 g) and EtOAc (15 g) soluble fractions. The EtOAc soluble fraction was fractionated by VLC (Si gel 150 g; eluents *n*-hexane-EtOAc 9:1, 4:1, 7:3 and 1:1) into four fractions A-D. Purification of fraction A (1.9 g) by CPC (eluents: *n*-hexane-EtOAc 9:1, 17:3 and 4:1) gave compound **2** (10 mg, 0.0015%) and a fraction (1.2 g), which on purification by the same method (eluents: *n*-hexane-$CHCl_3$ 2:3, 1:1 and 3:2), yielded compounds **1** (120 mg, 0.018%), **3** (11 mg, 0.0017%), and **4** (17 mg, 0.0026%). Two steps purification of fraction B (1,7 g) using CPC (first eluents: *n*-hexane-acetone 4:1 and 7:3; second eluents *n*-hexane-acetone 9:1 and 4:1) gave compounds **8** (40 mg, 0.0061%), **9** (57 mg, 0.0086%) and **10** (35 mg, 0.0053%). The same method was also applied to purify fraction C (1.9 g) (eluent: *n*-hexane-$CHCl_3$ 1:4) to give compound **5** (480 mg, 0.0738%). CPC purification on fraction D (850 mg) (two steps; first eluents: *n*-hexane-EtOAc 7:3 and 2:3; second eluents: *n*-hexane-$CHCl_3$ 1:4 and $CHCl_3$-EtOAc 9:1) yielded compounds **6** (6 mg, 0.0009%) and **7** (45 mg, 0.0069%).

2.4. 4′-O-Methylmacagigantin (4)

Pale yellow solid; IR (KBr) ν_{max}: 3350 (OH), 2970, 2918 (alkyl-CH), 1649 (conj. C=O), 1606, 1560 (aromatic C=C), 1230, 1180, (C–O), 835, 819, 802 (alkene C=C) cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz) see Table 1; HRESIMS *m/z* $[M-H]^-$ 503.2438 (calcd $[M-H]^-$ for $C_{31}H_{36}O_6$, 503.2434).

2.5. Macatrichocarpin F (5)

Pale yellow solid; ^1H NMR ($CDCl_3$, 500 MHz) see Table 2; ^{13}C NMR ($CDCl_3$, 125 MHz) see Table 2; HRESIMS *m/z* $[M + H]^+$ 365.2102 (calcd $[M + H]^+$ for $C_{24}H_{28}O_3$, 365.2111).

2.6. Macatrichocarpin G (6)

Pale yellow solid; ^1H NMR (acetone-d_6, 500 MHz) see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz) see Table 1; HRESIMS *m/z* $[M + H]^+$ 381.2058 (calcd $[M + H]^+$ for $C_{24}H_{28}O_4$, 381.2060).

Table 1
^1H and ^{13}C NMR data of 4′-*O*-methylmacagigantin (**4**) in acetone-d_6.

No	δ_H (*mult.*, *J* in Hz)	δ_C	No	δ_H (*mult.*, *J* in Hz)	δ_C
2	–	145.6	1”	3.47 (*d*, 6.7)	21.6
3	–	135.9	2”	5.29 (*tm*, 6.7)	121.1
4	–	175.4	3”	–	139.9
4a	–	103.7	4”	1.96 (*br t*, 7.3)	39.9
5	–	157.8	5”	2.13 (*br q*, 7.3)	26.4
6	–	109.6	6”	5.07 (*tm*, 6.8)	123.7
7	–	161.9	7”	–	135.9
8	6.62 (*s*)	94.5	8”	2.10 (*br t*, 7.3)	39.8
8a	–	155.2	9”	2.03 (*br q*, 7.3)	26.8
1’	–	123.5	10”	5.07 (*tm*, 6.8)	124.5
2′/6’	8.15 (*d*, 8.6)	129.5	11”	–	131.5
3′/5’	7.02 (*d*, 8.6)	114.2	12”	1.66 (*br s*)	25.9
4’	–	161.2	13”	1.55 (*br s*)	16.2
5-OH	12.10 (*s*)	–	14”	1.55 (*br s*)	17.9
4′-OCH_3	3.80 (*s*)	55.6	15”	1.84 (*br s*)	16.4

2.7. Macatrichocarpin H (7)

Pale yellow solid; IR (KBr) ν_{max}: 3412 (OH), 2924, 2855 (alkyl-CH), 1601, 1518 (aromatic C=C), 1140 (C–O), 960, 806 (alkene C=C) cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz) see Table 1; HRESIMS *m/z* $[M-H]^-$ 379.1911 (calcd $[M-H]^-$ for $C_{24}H_{28}O_4$, 379.1909).

2.8. cytotoxicity assay

Cytotoxic properties of the isolated compounds **1–10** against murine leukemia P-388 cells was done using MTT assay as previously described [7], with artonin E was used as the positive control.

3. Results and discussion

Compounds **1–3** were identified based on comparison of their NMR data with those previously reported [5,8]. 4′-*O*-Methylmacagigantin (**4**) has a molecular formula $C_{31}H_{36}O_6$ based on HRESIMS measurement ($[M-H]^-$: found *m/z* 503.2438, calcd *m/z* 503.2434). The IR absorptions showed vibrations for –OH (3350 cm^{-1}), alkyl C–H (2970, 2918 cm^{-1}). conjugated C=O (1649 cm^{-1}), aromatic C=C (1606,