New flavonoid and stilbene derivatives from the fruits of Macaranga balansae

Huong Doan Thi Mai, Thang Pham Toan, Giap Tran Huu, Thanh Nguyen Le, Vu Thi Kim Oanh, Nguyen Thi Minh Hang, Huong Tran Thu, van Minh Chau, Marc Litaudon, van Cuong Pham

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Macaranga balansae

1. \( \text{IC}_{50} = 29.51 \mu M \) (A549)

2. \( \text{IC}_{50} = 10.86 \mu M \) (A549)
   \( \text{IC}_{50} = 17.89 \mu M \) (Pan C1)
   \( \text{IC}_{50} = 17.84 \mu M \) (KB)
   \( \text{IC}_{50} = 22.81 \mu M \) (Lu-1)

3. \( \text{IC}_{50} = 26.73 \mu M \) (A549)
New flavonoid and stilbene derivatives from the fruits of *Macaranga balansae*

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New flavonoid and stilbene derivatives from the fruits of *Macaranga balansae*

Two new prenylated flavonoids, 4′-methyl-8-prenyltaxifolin (1) and 6,8-diprenyl-4′-methyl-narigenin (2) and a new geranylated stilbene, 4′-deprenyl-4-methoxymappain (3) together with eight known flavonoids (4-11) were isolated from the fruits of *Macaranga balansae* Gagnep. Their chemical structures were determined by means of spectroscopic methods including 1D, 2D NMR, and MS data. Compound 2 showed the highest cytotoxic activity against PanC1, A549, KB and LU-1 cell lines with IC<sub>50</sub> values range from 7.89 to 22.91 µM.

Keywords: *Macaranga balansae*, Euphorbiaceae, prenylated flavonoid, stilbene, cytotoxic activity.

1. Introduction

*Macaranga* is a large genus of the Euphorbiaceae family, comprising more than 300 species and widely distributed in the tropical regions (Yang et al. 2015). In Vietnam, this genus known as “marang” has been used in the traditional medicine for the treatment of swellings, wounds and diarrhea (Vo 2012; Pham et al.1999). Previous studies on chemistry and pharmacology of *Macaranga* genus showed that their crude extracts and isolated compounds displayed interesting bioactivities such as antioxidant, antitumor, antimicrobial, and anti-inflammatory effects (Yoder et al. 2007, Magadula 2014). Flavonoids and stilbenes are major constituents and are most likely responsible for most of the activities found in the plants of this genus (Magadula 2014; Yang et al. 2015; Tanjung et al. 2018).

*Macaranga balansae* Gagnep is a native tree distributed in the central provinces of Vietnam. The chemical constituents of this plant have not been studied yet. In continuing of our study on anticancer effects of *Macaranga* genus in Vietnam (Péresse et al. 2017; Trinh et al. 2012), herein we report the isolation and structural elucidation of two new prenylated flavonoids, 4′-methyl-8-prenyltaxifolin (1), 6,8-diprenyl-4′-methylnarigenin (2), one new geranylated stilbene, 4′-deprenyl-4-methoxymappain (3) and eight known flavonoids (4-11) from the fruits of *M. balansae* (Fig. 1). Their chemical structures were established based on IR, NMR, and HR-ESI-MS spectra analysis. All newly isolated compounds were evaluated for cytotoxic activity.

2. Results and discussions

Compound 1 was isolated as colourless solid. The molecular formula of C<sub>21</sub>H<sub>22</sub>O<sub>7</sub> was determined from the peak at m/z 385.1285 [M-H]<sup>-</sup> in the negative HR-ESI-MS of 1. The IR spectrum showed hydroxyl and carbonyl absorptions at 3443 and 1634 cm<sup>-1</sup>. The 1H-NMR
The HMBC correlations from H-2' (δH 7.09)/H-6' (δH 7.02) to C-4' (δC 147.7); from H-5' (δH 6.92) to C-3' (δC 145.9); from methoxy protons (δH 3.91) to C-4' (δC 147.7) suggested the positions of hydroxy and methoxy groups at C-3' and C-4', respectively. The HMBC correlations between H-2'' (δH 5.18) to C-8 (δC 108.7)/C-1'' (δC 21.5)/C-4'' (δC 25.7)/C-5'' (δC 17.6); between H-1'' (δH 3.19) to C-7 (δC 165.5)/C-8 (δC 147.7)/C-8a (δC 159.9) suggested the position of prenyl group at C-8 (Fig. S1). The 2,3-trans configuration was assigned from the large coupling constant value of H-2 and H-3 (J = 12.0 Hz). In addition, the absolute configuration at C-2 were determined to be R from the positive Cotton effect at 340 nm and the negative one at 296 nm in the CD spectrum, similar to those of related compound (Sasaki et al. 2014; Suthivaiyakit et al. 2009). Thus, the absolute configuration of 1 was characterised as 2R,3R (Wu et al. 2003; Slade et al. 2005). Compound 1 was newly identified as 4'-methyl-8-prenyltaxifolin.

Compound 2 was obtained as pale yellow solid. Its HR-ESI-MS ion at m/z 423.2179 [M+H]+ corresponding to the molecular formula of C26H31O5. The 1H- and 13C-NMR data of compound 2 were very similar to those of lonchocarpol A (Meragelman et al. 2011). The only difference is 2 containing a methoxy group in the NMR spectrum. In the 1H-NMR spectrum, the signals at δH 5.34 (dd, J = 12.5, 3.0 Hz), 3.07 (dd, J = 17.5, 12.5 Hz) and 2.82 (dd, J = 17.0, 3.0 Hz), suggested the presence of flavanone skeleton. In addition, the signals at δH 3.30 (2H, d, J = 7.0 Hz, H-1''), 5.21 (1H, t, J = 7.0 Hz, H-2''), 1.70 (3H, s, H-4''), 1.71 (3H, s, H-5''), 3.35 (2H, d, J = 7.0 Hz, H-1'''), 5.25 (1H, t, J = 7.0 Hz, H-2'''), 1.81 (3H, s, H-4'''), 1.74 (3H, s, H-5'''') were assigned to two prenyl groups. The HMBC correlations between H-1'' and C-7 (δC 162.2)/C-8 (δC 106.4)/C-8a (δC 157.7); between H-1'''' and C-5 (δC 159.3)/C-6 (δC 107.2)/C-7 (δC 162.2) confirming the positions of prenyl groups at C-8 and C-6. The methoxy group at C-4' were confirmed by HMBC correlation from the methoxy group (δH 3.83) to C-4' (δC 159.8) (Fig. S1). Consequently, compound 2 was identified as 6,8-diprenyl-4'-methylnarigenin.

Compound 3 was obtained as pale yellow solid. Its molecular
formula was determined as C_{25}H_{30}O_{4} by HR-ESI-MS (m/z 395.2222, [M+H]^+), calcd. for 395.2222). The chemical structure of 3 is similar to 4'-deprenyl-mappain isolated from *African propolis* (Almutairi et al. 2014). The only difference is 3 containing a methoxy group (δ_{H} 3.80, δ_{C} 61.3) in the NMR spectrum. The ¹H-NMR spectrum of 3 showed signals of a geranylated trans-stilbene (J = 16.0 Hz) with two olefinic protons observed at δ_{H} 6.90 (d, J = 16.0 Hz, H-α) and 6.80 (d, J = 16.0 Hz, H-β). The HMBC correlations from H-β (δ_{H} 6.80) to C-1′ (δ_{C} 133.8), C-2′(C-6′) (δ_{C} 106.1); from H-2′ (H-6′) (δ_{H} 6.53) to C-3′ (C-5′) (δ_{C} 156.9) and C-4′ (δ_{C} 102.1) suggested the positions of two hydroxy groups at C-3′ and C-5′. The HMBC correlations from H-6 (δ_{H} 6.96) to C-α (δ_{C} 129.1)/C-4 (δ_{C} 145.0); from H-2 (δ_{H} 6.80) to C-α (δ_{C} 129.1)/C-3 (δ_{C} 134.8); and from methoxy group (δ_{H} 3.80) to C-4 (δ_{C} 145.0) confirmed the position of methoxy and hydroxy groups at C-4 and C-5, respectively. The geranyl group was characterized by three methyl groups at δ_{H} 1.74, 1.59, and 1.66 (3H, each, s); three methylene signals at δ_{H} 3.37 (d, J = 6.5 Hz), 2.12 (7, J = 8.0 Hz) and 2.07 (t, J = 7.5 Hz); two olefinic protons at δ_{H} 5.30 (t, J = 7.0 Hz) and 5.10 (d, J = 6.0 Hz). The locations of geranyl at C-3 of benzene ring was determined by the HMBC correlations from H-1′′ (δ_{H} 3.37) to C-2 (δ_{C} 120.5)/C-3 (δ_{C} 134.8)/C-4 (δ_{C} 145.0); from H-2 (δ_{H} 6.80) to C-1′′ (δ_{C} 28.0) (Fig. S1). Thus, the structure of compound 3 was elucidated as 4'-deprenyl-4-methoxymappain.

The known compounds were elucidated as 8-prenylisosacuranetin (4) (Chen et al. 2013), lonchocarpol A (5) (Meragelman et al. 2011), 6,8-diprenylaromadendrin (Meragelman et al. 2011) (6), propolin I (7) (Huang et al. 2010), exiguaflavanone K (8) (Linuma et al. 1994), 8-prenynarigenin (9) (Chen et al. 2013), 5,7,4′-trihydroxy-8-(2,3-dihydroxy-3-methylbutyl)flavanone (10) (Cano et al. 2006), and macarecurvatin A (11) (Tanjung et al. 2014). Their chemical structures were determined by NMR spectra and in comparison with previously reported values. Notably, propolin I (7) have been only isolated from Taiwanese propolis, not from any plant (Huang et al. 2010).

Compounds 1-3 were evaluated for their cytotoxicity against seven cancer cell lines including A549, Hela, Pan C1, MCF-7, Hep3B, KB and Lu-1 using MTT method (Mosmann 1983). As the results, compound 2 showed significant cytotoxicity against A549, PanC1, KB and Lu-1 cancer cell lines with IC_{50} values range from 7.89 to 22.81 µM while compound 1 and 3 displayed the moderate activity against A549, Hela, Pan C1, MCF-7, Hep3B cell lines (IC_{50} values range from 26.73 to 79.43 µM) (Table S1).
3. Experimental

3.1. General experimental procedures

Optical rotations were recorded on a Polax-2L polarimeter in CHCl₃. HR-ESI-MS were recorded on a FT-ICR 910-MS TQFTMS-7T and a VARIAN 910 mass spectrometers. IR spectra were recorded on a Nicolet Impact 410 FT-IR spectrometer, UV spectrum on a UV-1601 spectrometer, and NMR spectra on a Bruker AM500 MHz spectrometer operating at 125.76 MHz for ¹³C NMR, and at 500.13 MHz for ¹H-NMR. ¹H-NMR chemical shifts were referenced to CDCl₃ at 7.27 ppm, and ¹³C-NMR chemical shifts to the central peak of CDCl₃ at 77.0 ppm.

3.2 Plant material

The fruits of *M. balansae* Gagnep. were collected at Tuyen Hoa, Quang Binh, in 2011, July and identified by Dr. Nguyen The Cuong, Institute of Ecology and Biological Resources, Vietnam Academy of Science & Technology. A voucher specimen (VN-2223) was deposited at the Herbarium of the Institute of Ecology and Biological Resources, VAST.

3.3 Extraction and isolation

The powdered, dried fruits of *M. balansae* Gagnep. (200 g) was extracted with ethyl acetate (1 L x 4 times, 24h/time) at room temperature. The combined extracts were evaporated *in vacuo* to obtain ethyl acetate residue (20 g). The ethyl acetate residue was purified by chromatography column (CC) on silica gel and eluted with solvent gradient of n-hexane/acetone to afford 17 fractions (E1-E17). Fraction E4 (0.27 g) was separated on silica gel CC, eluted with n-hexane-CH₂Cl₂ (8:2, v/v) to yield 2 (22 mg). Fraction E12 (5 g) was recrystallized in CH₂Cl₂ to give 4 (40 mg). Fraction E12 (3.57 g) was subjected to silica gel CC and eluted with n-hexane/ethyl acetate (7:3, v/v) to give 7 sub-fractions E12.1-E12.7. Sub-fraction E12.1 (0.2 g) was separated by CC on silica gel, eluting with n-hexane/ethyl acetate (19:1, v/v) to afford 5 (9 mg). Sub-fraction E12.5 (0.5 g) was chromatographed on silica gel column and eluted with n-hexane/ethyl acetate (9:1, v/v) to give 3 sub-subfractions E12.5.1-E12.5.3. Fraction E12.5.3 (80 mg) was purified on silica gel CC using n-hexane/acetone (8:2, v/v) as eluent to yield 6 (8 mg). Fraction E13 (1.4 g) was purified on Sephadex LH-20 CC, eluted with MeOH/CH₂Cl₂ (8:2, v/v) to afford 2 sub-fractions E13.1-E13.2. Sub-fraction E13.2 (0.5 g) was separated on silica gel CC and eluting was performed with n-hexane/acetone (7:3, v/v) yield 7. Fraction E14 (1.6 g) was chromatographed on silica gel column eluting with CH₂Cl₂/acetone (9:1, v/v) to give 2 sub-fractions E14.1-E14.2. Compound 8 (9 mg) and 9 (4.5 mg) was obtained from the E14.1 and E14.2 sub-fractions, respectively by recrystallization in CH₂Cl₂. Fraction E17 (2.4 g) was separated by Sephadex CC and eluted with MeOH/CH₂Cl₂ (8:2, v/v) to give 3 sub-fractions.
E17.1-E17.3. Sub-fraction E17.1 (60 mg) was purified with silica gel CC and eluted with CH$_2$Cl$_2$/acetone (8:2, v/v) to afford 2 sub-subfraction E12.1.1-E17.1.2. Fraction E17.1.1 (18 mg) was purified on Sephadex CC, eluting was performed with MeOH/CH$_2$Cl$_2$ (8:2, v/v) to yield 10 (2.5 mg). Subfraction E17.1.2 (22 mg) was separated by preparative silica gel TLC using CH$_2$Cl$_2$/acetone (19:1, v/v) as eluent to give compound 1 (4.5 mg). Sub-fraction E17.3 (53 mg) was separated on silica gel CC and eluted with CH$_2$Cl$_2$/acetone (9:1, v/v) to yield 11 (26 mg) and 3 (8.5 mg).

3.3.1. 4´-Methyl-8-prenyltaxifolin (1)

Colorless solid; [α]$_{25}^{20}$ = 20.0 (c 0.04, CHCl$_3$); UV (MeOH) $\lambda_{\text{max}}$ 295, 342 nm; FT-IR (KBr) $\nu_{\text{max}}$: 3443, 2929, 1634, 1444, 1384 cm$^{-1}$; $^1$H-NMR and $^{13}$C-NMR data see Table 1; HR-ESI-MS: m/z 385.1285 [M-H]$^-$ (calcd. for C$_{21}$H$_{21}$O$_7$, 385.1287).

3.3.2. 6,8-Diprenyl-4´-methyl-narigenin (2)

Pale yellow oil; [α]$_{24}^{20}$ = 23.6 (c 0.15, CHCl$_3$); UV (MeOH) $\lambda_{\text{max}}$ 295, 342 nm; FT-IR (KBr) $\nu_{\text{max}}$: 3438, 2917, 2852, 1633, 1516, 1448, 1342, 1376, 1306, 1178, 1118 cm$^{-1}$; $^1$H- and $^{13}$C-NMR data see Table 1; HR-ESI-MS: m/z 423.2179 [M + H]$^+$ (calcd. for C$_{26}$H$_{31}$O$_5$, 423.2171).

3.3.3. 4´-Deprenyl-4-methoxymappain (3)

Pale yellow solid; UV (MeOH) $\lambda_{\text{max}}$ 305, 340 nm; FT-IR (KBr) $\nu_{\text{max}}$: 3443, 2929, 1628, 1445, 1382, 1144, 1001, 847 cm$^{-1}$; $^1$H- and $^{13}$C-NMR data see Table 1; HR-ESI-MS: m/z 395.2222 [M + H]$^+$ (calcd. for C$_{25}$H$_{30}$O$_4$, 395.2222).

3.4 Cytotoxic activity assay

The cytotoxicity assays were carried out in triplicate in 96-well microtiter plates against A549, Hela, PanC1, MCF-7, Hep3B, KB and Lu-1 cell lines. Cells were maintained in Dulbecco’s D-MEM medium, supplemented with 10% fetal calf serum, L-glutamine (2 mM), penicillin G (100 UI/mL), streptomycin (100 µg/mL) and gentamicin (10 µg/mL). Stock solutions of compounds were prepared in DMSO/H$_2$O (1/9), and the cytotoxicity assays were carried out in 96-well microtiter plates against cancer or normal cells (3 x 10$^3$ cells/mL) using a modification of the published method (Mosmann T. 1983). After 72 h incubation at 37 °C in air/CO$_2$ (95:5) with or without test compounds, cell growth was estimated by colorimetric measurement of stained living cells by neutral red. Optical density was determined at 540 nm with a Titertek Multiskan photometer. The IC$_{50}$ value was defined as the concentration of sample necessary to inhibit the cell growth to 50% of the control. Ellipticine was used as a reference compound.
4. Conclusion

Two new flavonoids, 4´-methyl-8-prenyltaxifolin (1) and 6,8-diprenyl-4´-methyl-narigenin (2) and a new geranylated stilbene 4´-deprenyl-4-methoxymappain (3) together with eight known compounds (4-11) were isolated from the fruits of M. balansae Gagnep. collected in Quang Binh province, Vietnam. Compound 2 exhibited significant cytotoxicity against A549, PanC1, KB and Lu-1 cancer cell lines with IC$_{50}$ values range from 7.89 to 22.81 µM.

Supplementary material

HR-ESI-MS, 1D, 2D NMR spectra and cytotoxicity results of compounds 1-3, are available as Supporting Information.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Figure 1. Chemical structures of 1-11 from *M. balansae*
Table 1. The NMR spectral data of compounds 1-3

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*a Measured in CDCl$_3$ and CD$_3$OD, b Measured in CDCl$_3$
New flavonoid and stilbene derivatives from the fruits of *Macaranga balansae*

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lethanh@imbc.vast.vn (Thanh Nguyen Le)
Figure S1. Key HMBC correlations of 1-3

Table S1. Cytotoxicity of isolated compounds 1-3

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<th>Compound</th>
<th>A549 (µM)</th>
<th>Hela (µM)</th>
<th>MCF-7 (µM)</th>
<th>Hep3B (µM)</th>
<th>Pan C1 (µM)</th>
<th>KB (µM)</th>
<th>LU-1 (µM)</th>
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na: not active
Figure S2. HR-MS spectrum of compound 1

Figure S3. IR spectrum of compound 1
Figure S4. $^1$H-NMR spectrum of compound 1

Figure S5. $^{13}$C-NMR spectrum of compound 1
Figure S6. $^{13}$C-DEPT spectrum of compound 1

Figure S7. COSY spectrum of compound 1
Figure S8. HSQC spectrum of compound 1

Figure S9. HMBC spectrum of compound 1
Figure S10. CD spectrum of compound 1

Figure S11. HR-MS spectrum of compound 2
Figure S12. IR spectrum of compound 2

Figure S13. $^1$H-NMR spectrum of compound 2
Figure S14. $^{13}$C-NMR spectrum of compound 2

Figure S15. COSY spectrum of compound 2
Figure S16. HSQC spectrum of compound 2

Figure S17. HMBC spectrum of compound 2
Figure S18. HR-MS spectrum of compound 3

Figure S19. IR spectrum of compound 3
Figure S20. $^1$H-NMR spectrum of compound 3

Figure S21. $^{13}$C-NMR spectrum of compound 3
Figure S22. COSY spectrum of compound 3

Figure S23. HSQC spectrum of compound 3
Figure S24. HMBC spectrum of compound 3