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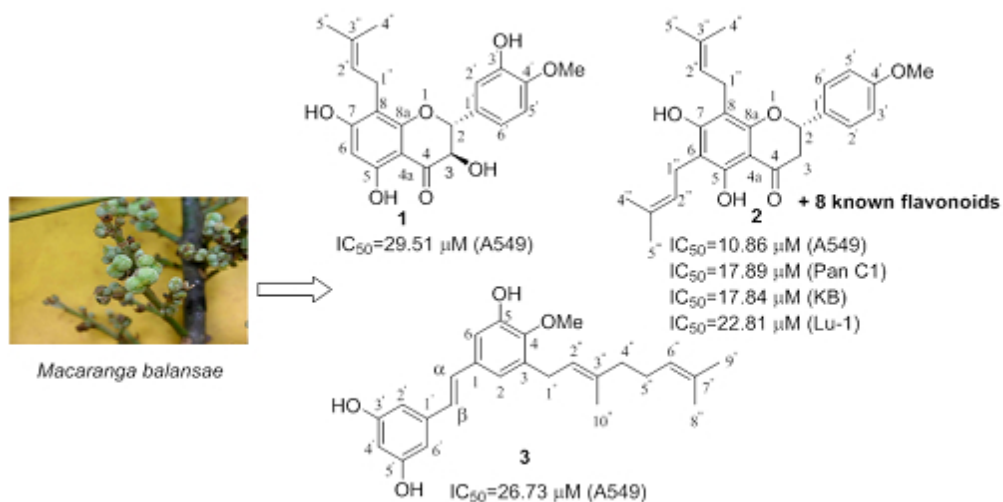
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New flavonoid and stilbene derivatives from the fruits of *Macaranga balansae*

Huong Doan Thi Mai^{a,b*}, Thang Pham Toan^{c,d}, Giap Tran Huu^a, Thanh Nguyen Le^{a,b*}, Vu Thi Kim Oanh^a, Nguyen Thi Minh Hang^a, Huong Tran Thu^c, Van Minh Chau^a, Marc Litaudon^e, Van Cuong Pham^{a,b}

^a*Advanced Center for Bioorganic Chemistry, Institute of Marine Biochemistry, Vietnam Academy of Science and Technology (VAST), 18 Hoang Quoc Viet, Caugiay, Hanoi, Vietnam;*

^b*Graduate University of Science and Technology, VAST, 18 Hoang Quoc Viet, Caugiay, Hanoi, Vietnam;*

^c*School of Chemical Engineering, Hanoi University of Science and Technology, 1 Dai Co Viet, Ha Ba Trung, Hanoi, Vietnam;*

^d*Institute of Forensic Sciences, Ministry of Public Security, 99 Nguyen Tuan, Thanh Xuan, Hanoi, Vietnam;*

^e*Institut de Chimie des Substances Naturelles, 91190 Gif-sur-Yvette Cedex, France;*

* Corresponding author:

Assoc Prof. Dr. Huong Doan Thi Mai and Dr. Thanh Nguyen Le

Institute of Marine Biochemistry

Vietnam Academy of Science and Technology

18 Hoang Quoc Viet, Caugiay, Hanoi, Vietnam

Tel.: 8424 37564995

Fax: 8424 7917054

E-mail address: huongdm@imbc.vast.vn (Huong Doan Thi Mai);

lethanh@imbc.vast.vn (Thanh Nguyen Le)

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 IC₅₀ values range from 7.89 to 22.91 μ M.

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 C₂₁H₂₂O₇ was determined from the peak at *m/z* 385.1285 [M-H]⁻ in the negative HR-ESI-MS of **1**. The IR spectrum showed hydroxyl and carbonyl absorptions at 3443 and 1634 cm⁻¹. The ¹H-NMR

spectrum of **1** showed characteristic signals of a flavanonol with an ABX aromatic system of B ring (δ_{H} 7.09 (d, $J = 2.0$ Hz, H-2'), 7.02 (dd, $J = 8.5, 2.0$ Hz, H-6'), 6.92 (d, $J = 8.0$ Hz, H-5'), two oxymethine protons [δ_{H} 4.96 (d, $J = 12.0$ Hz) and 4.48 (d, $J = 12.0$ Hz)] of C-ring, and signals of a prenyl group at δ_{H} 5.18 (1H, t, $J = 7.0$ Hz), 3.19 (2H, d, $J = 7.0$ Hz), 1.64 (3H, s), and 1.57 (3H, s). In addition, one methoxy group was observed at δ_{H} 3.91 (s). The ^{13}C -NMR spectrum of **1** showed the signals of 21 carbon including fifteen carbons of flavanonol and five carbons of a prenyl and one methoxy carbon (δ_{C} 56.0). The above evidence suggested that the structure of **1** was similar to 8-prenyltaxifolin except for the presence of methoxy group at C-4' (Chen et al. 2013). The HMBC correlations from H-2' (δ_{H} 7.09)/H-6' (δ_{H} 7.02) to C-4' (δ_{C} 147.7); from H-5' (δ_{H} 6.92) to C-3' (δ_{C} 145.9); from methoxy protons (δ_{H} 3.91) to C-4' (δ_{C} 147.7) suggested the positions of hydroxy and methoxy groups at C-3'' and C-4'', respectively. The HMBC correlations between H-2'' (δ_{H} 5.18) to C-8 (δ_{C} 108.7)/C-1'' (δ_{C} 21.5)/C-4'' (δ_{C} 25.7)/C-5'' (δ_{C} 17.6); between H-1'' (δ_{H} 3.19) to C-7 (δ_{C} 165.5)/C-8 (δ_{C} 147.7)/C-8a (δ_{C} 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; Sutthivaiyakit et al. 2009). Thus, the absolute configuration of **1** was characterised as 2*R*,3*R* (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 $[\text{M}+\text{H}]^+$ corresponding to the molecular formula of $\text{C}_{26}\text{H}_{31}\text{O}_5$. The ^1H - and ^{13}C -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 δ_{H} 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 δ_{H} 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 (δ_{C} 162.2)/C-8 (δ_{C} 106.4)/C-8a (δ_{C} 157.7); between H-1''' and C-5 (δ_{C} 159.3)/C-6 (δ_{C} 107.2)/C-7 (δ_{C} 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 (δ_{H} 3.83) to C-4' (δ_{C} 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

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2 formula was determined as $C_{25}H_{30}O_4$ by HR-ESI-MS (m/z 395.2222, $[M+H]^+$, calcd. for
3 395.2222). The chemical structure of **3** is similar to 4'-deprenyl-mappain isolated from *African*
4 *propolis* (Almutairi et al. 2014). The only difference is **3** containing a methoxy group (δ_H 3.80,
5 δ_C 61.3) in the NMR spectrum. The 1H -NMR spectrum of **3** showed signals of a geranylated
6 *trans*-stilbene ($J = 16.0$ Hz) with two olefinic protons observed at δ_H 6.90 (d, $J = 16.0$ Hz, H- α)
7 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-
8 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)
9 suggested the positions of two hydroxy groups at C-3' and C-5'. The HMBC correlations from H-
10 6 (δ_H 6.96) to C- α (δ_C 129.1)/C-4 (δ_C 145.0)/C-5 (δ_C 148.9); from H-2 (δ_H 6.80) to C- α (δ_C
11 129.1)/C-3 (δ_C 134.8); and from methoxy group (δ_H 3.80) to C-4 (δ_C 145.0) confirmed the
12 position of methoxy and hydroxy groups at C-4 and C-5, respectively. The geranyl group was
13 characterized by three methyl groups at δ_H 1.74, 1.59, and 1.66 (3H, each, s); three methylene
14 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
15 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
16 benzene ring was determined by the HMBC correlations from H-1'' (δ_H 3.37) to C-2 (δ_C
17 120.5)/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
18 structure of compound **3** was elucidated as 4'-deprenyl-4-methoxymappain.

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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-
prenylnarigenin (**9**) (Chen et al. 2013), 5,7,4'-trihydroxy-8-(2,3-dihydroxy-3-
methylbutyl)flavanone (**10**) (Cano et al. 2006), and macarecurvatins 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 CHCl_3 . 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 ^{13}C NMR, and at 500.13 MHz for ^1H -NMR. ^1H -NMR chemical shifts were referenced to CDCl_3 at 7.27 ppm, and ^{13}C -NMR chemical shifts to the central peak of CDCl_3 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- CH_2Cl_2 (8:2, v/v) to yield **2** (22 mg). Fraction E12 (5 g) was recrystallized in CH_2Cl_2 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-E.12.5.3. Fraction E.12.5.3 (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 $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (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 CH_2Cl_2 /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 CH_2Cl_2 . Fraction E17 (2.4 g) was separated by Sephadex CC and eluted with $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (8:2, v/v) to give 3 sub-fractions

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2 E17.1-E17.3. Sub-fraction E17.1 (60 mg) was purified with silica gel CC and eluted with
3 CH₂Cl₂/acetone (8:2, v/v) to afford 2 sub-subfraction E12.1.1-E17.1.2. Fraction E17.1.1 (18 mg)
4 was purified on Sephadex CC, eluting was performed with MeOH/CH₂Cl₂ (8:2, v/v) to yield **10**
5 (2.5 mg). Subfraction E17.1.2 (22 mg) was separated by preparative silica gel TLC using
6 CH₂Cl₂/acetone (19:1, v/v) as eluent to give compound **1** (4.5 mg). Sub-fraction E17.3 (53 mg)
7 was separated on silica gel CC and eluted with CH₂Cl₂/acetone (9:1, v/v) to yield **11** (26 mg) and
8 **3** (8.5 mg).
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14 3.3.1. 4'-Methyl-8-prenyltaxifolin (**1**)

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16 Colorless solid; $[\alpha]_D^{25} - 20.0$ (c 0.04, CHCl₃); UV (MeOH) λ_{\max} 295, 342 nm; FT-IR (KBr) ν_{\max} :
17 3443, 2929, 1634, 1444, 1384 cm⁻¹; ¹H-NMR and ¹³C-NMR data see Table 1; HR-ESI-MS: m/z
18 385.1285 [M-H]⁻ (calcd. for C₂₁H₂₁O₇, 385.1287).
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22 3.3.2. 6,8-Diprenyl-4'-methyl-narigenin (**2**)

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24 Pale yellow oil; $[\alpha]_D^{24} - 23.6$ (c 0.15, CHCl₃); UV (MeOH) λ_{\max} 295, 342 nm; FT-IR (KBr) ν_{\max} :
25 3438, 2917, 2852, 1633, 1516, 1448, 1342, 1376, 1306, 1253, 1178, 1118 cm⁻¹; ¹H- and ¹³C-
26 NMR data see Table 1; HR-ESI-MS: m/z 423.2179 [M + H]⁺ (calcd. for C₂₆H₃₁O₅, 423.2171).
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30 3.3.3. 4'-Deprenyl-4-methoxymappain (**3**)

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32 Pale yellow solid; UV (MeOH) λ_{\max} 305, 340 nm; FT-IR (KBr) ν_{\max} : 3443, 2929, 1628, 1445,
33 1382, 1144, 1001, 847 cm⁻¹; ¹H- and ¹³C-NMR data see Table 1; HR-ESI-MS: m/z 395.2222 [M
34 + H]⁺ (calcd. for C₂₅H₃₀O₄, 395.2222).
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38 3.4 Cytotoxic activity assay

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40 The cytotoxicity assays were carried out in triplicate in 96-well microtiter plates against
41 A549, Hela, PanC1, MCF-7, Hep3B, KB and Lu-1 cell lines. Cells were maintained in
42 Dulbecco's D-MEM medium, supplemented with 10% fetal calf serum, L-glutamine
43 (2 mM), penicillin G (100 UI/mL), streptomycin (100 µg/mL) and gentamicin
44 (10 µg/mL). Stock solutions of compounds were prepared in DMSO/H₂O (1/9), and the
45 cytotoxicity assays were carried out in 96-well microtiter plates against cancer or normal
46 cells (3 x 10³ cells/mL) using a modification of the published method (Mosmann T.
47 1983). After 72 h incubation at 37 °C in air/CO₂ (95:5) with or without test compounds,
48 cell growth was estimated by colorimetric measurement of stained living cells by neutral
49 red. Optical density was determined at 540 nm with a Titertek Multiskan photometer. The
50 IC₅₀ value was defined as the concentration of sample necessary to inhibit the cell growth
51 to 50% of the control. Ellipticine was used as a reference compound.
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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 IC₅₀ 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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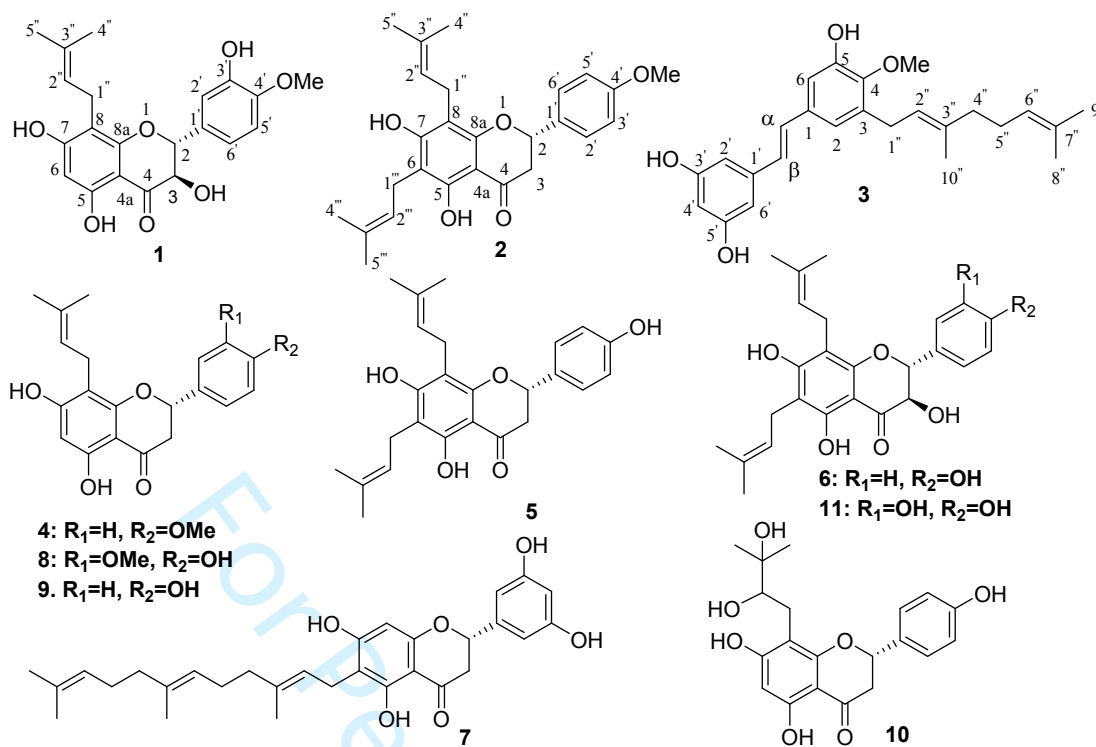


Figure 1. Chemical structures of **1-11** from *M. balansae*

Table 1. The NMR spectral data of compounds **1-3**

No	1^a		2^b		No	3^b	
	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)		δ_C	δ_H (J in Hz)
1					1	140.0	-
2	83.1	4.96 d (12.0)	78.5	5.34 dd (3.0, 12.5)	2	120.5	6.80 d (1.5)
3	72.5	4.48 d (12.0)	43.2	3.07 dd (12.5, 17.0) 2.82 dd (3.0, 17.0)	3	134.8	-
4	196.4	-	196.5	-	4	145.0	-
4a	100.5	-	102.8	-	5	148.9	-
5	161.2	-	159.3	-	6	110.7	6.96 d (1.5)
6	96.2	6.02 s	107.2	-	1'	133.8	-
7	165.5	-	162.2	-	2'	106.1	6.53 d (2.0)
8	108.7	-	106.4	-	3'	156.9	-
8a	159.9	-	157.7	-	4'	102.1	6.25 br s
1'	129.9	-	131.0	-	5'	156.9	-
2'	114.1	7.09 d (2.0)	127.4	7.37 d (8.5)	6'	106.1	6.53 d (2.0)
3'	145.9	-	114.0	6.95 d (8.5)	α	129.1	6.90 d (16.0)
4'	147.7	-	159.8	-	β	127.5	6.80 d (16.0)
5'	110.9	6.92 d (8.5)	114.0	6.95 d (8.5)	1''	28.0	3.37 d (7.0)
6'	119.6	7.02 dd (2.0, 8.5)	127.4	7.37 d (8.5)	2''	122.3	5.30 t (7.0)
1''	21.5	3.19 d (7.0)	21.2	3.30 d (7.0)	3''	136.6	-
2''	122.2	5.18 t (7.0)	122.0	5.21 t (7.0)	4''	39.6	2.07 t (7.5)
3''	131.8	-	133.8	-	5''	26.6	2.12 (m)
4''	25.7	1.64 s	17.9	1.70 s	6''	124.1	5.10 t (6.0)
5''	17.6	1.57 s	25.8	1.71 s	7''	131.7	-
1'''			21.9	3.35 d (7.0)	8''	25.7	1.74 s
2'''			121.8	5.25 t (7.0)	9''	17.7	1.59 s
3'''			134.6	-	10''	16.2	1.66 s
4'''			25.8	1.74 s	OMe	61.3	3.80 s
5'''			17.8	1.81 s			
OMe	56.0	3.91 s	55.3	3.83 s			
5-OH				12.33 s			
7-OH				6.36 s			

^aMeasured in $CDCl_3$ and CD_3OD , ^bMeasured in $CDCl_3$

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

Huong Doan Thi Mai^{a,b*}, Thang Pham Toan^{c,d}, Giap Tran Huu^a, Thanh Nguyen Le^{a,b*}, Vu Thi Kim Oanh^a, Nguyen Thi Minh Hang^a, Huong Tran Thu^c, Van Minh Chau^a, Marc Litaudon^e, Van Cuong Pham^{a,b}

^a*Advanced Center for Bioorganic Chemistry, Institute of Marine Biochemistry, Vietnam Academy of Science and Technology (VAST), 18 Hoang Quoc Viet, Caugiay, Hanoi, Vietnam;*

^b*Graduate University of Science and Technology, VAST, 18 Hoang Quoc Viet, Caugiay, Hanoi, Vietnam;*

^c*School of Chemical Engineering, Hanoi University of Science and Technology, 1 Dai Co Viet, Ha Ba Trung, Hanoi, Vietnam;*

^d*Institute of Forensic Sciences, Ministry of Public Security, 99 Nguyen Tuan, Thanh Xuan, Hanoi, Vietnam;*

^e*Institut de Chimie des Substances Naturelles, 91190 Gif-sur-Yvette Cedex, France;*

* Corresponding author:

Assoc Prof. Dr. Huong Doan Thi Mai and Dr. Thanh Nguyen Le

Institute of Marine Biochemistry

Vietnam Academy of Science and Technology

18 Hoang Quoc Viet, Caugiay, Hanoi, Vietnam

Tel.: 8424 37564995

Fax: 8424 7917054

E-mail address: huongdm@imbc.vast.vn (Huong Doan Thi Mai);

lethanh@imbc.vast.vn (Thanh Nguyen Le)

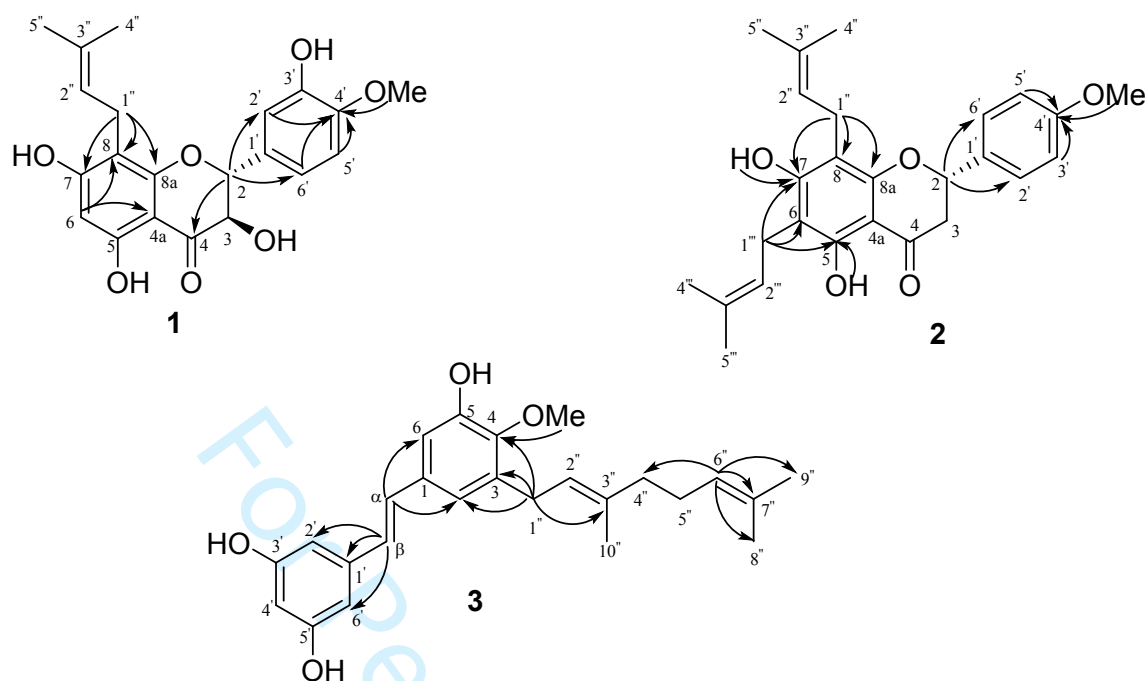
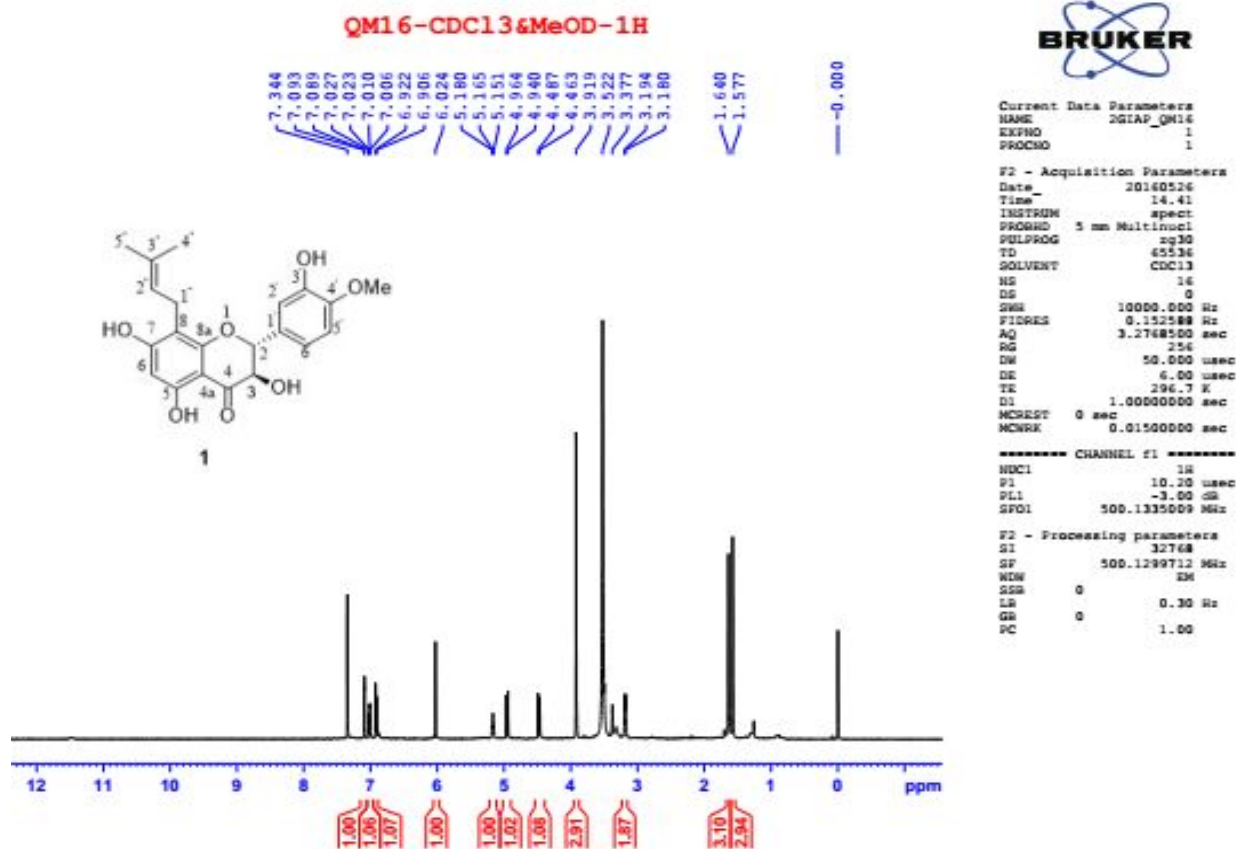
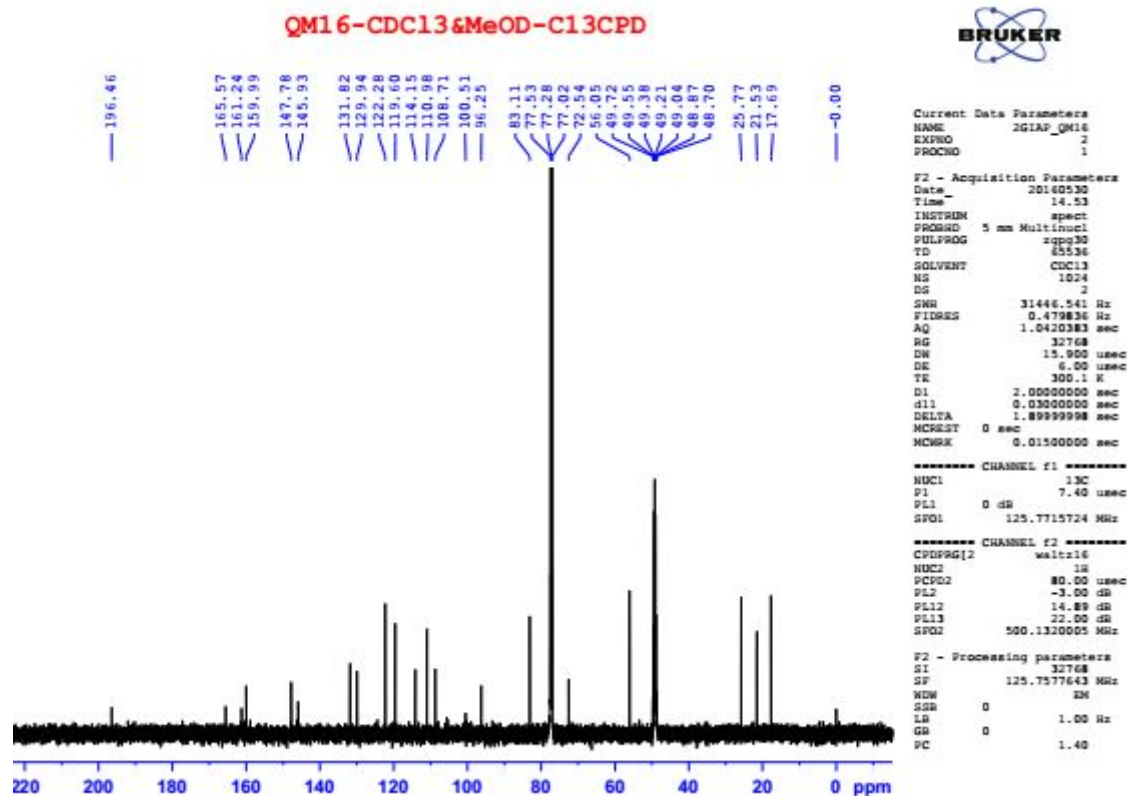


Figure S1. Key HMBC correlations of **1-3**

Table S1. Cytotoxicity of isolated compounds 1-3

Compound	IC ₅₀ (μM)						
	A549	Hela	MCF-7	Hep3B	Pan C1	KB	LU-1
1	29.51	48.98	53.09	<i>na</i>	64.27	<i>na</i>	<i>na</i>
2	10.86	54.95	<i>na</i>	<i>na</i>	7.89	17.84	22.81
3	26.73	40.09	50.93	79.43	54.95	<i>na</i>	<i>na</i>
Ellipticine	1.62	1.60	2.41	1.20	1.99	1.21	1.60

na: not active

Figure S4. ¹H-NMR spectrum of compound 1Figure S5. ¹³C-NMR spectrum of compound 1

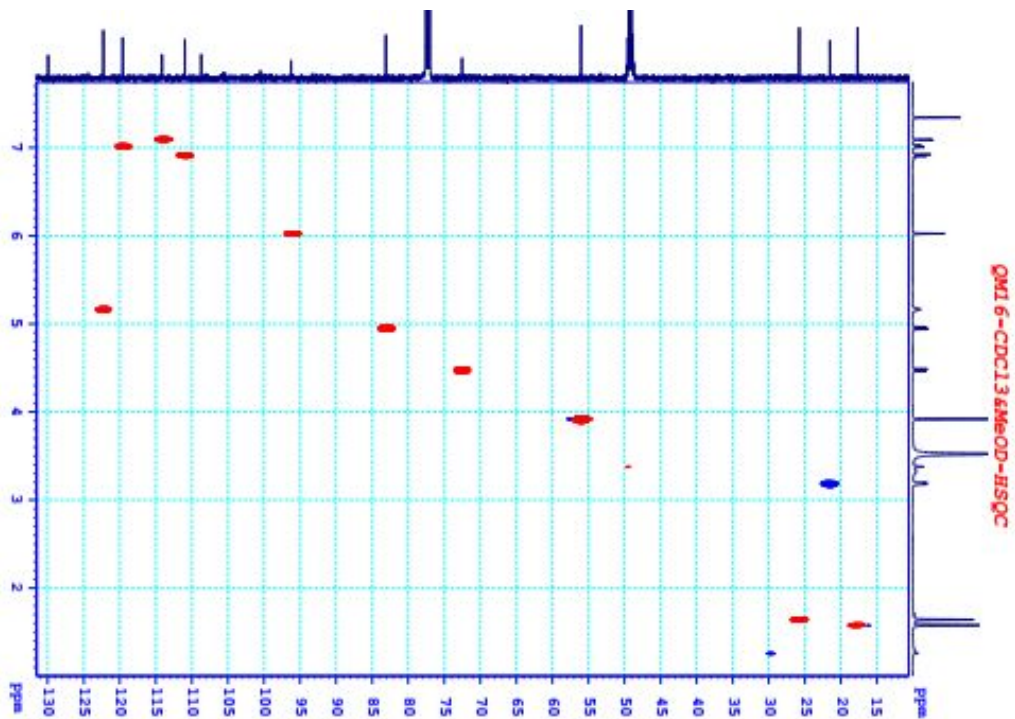


Figure S8. HSQC spectrum of compound 1

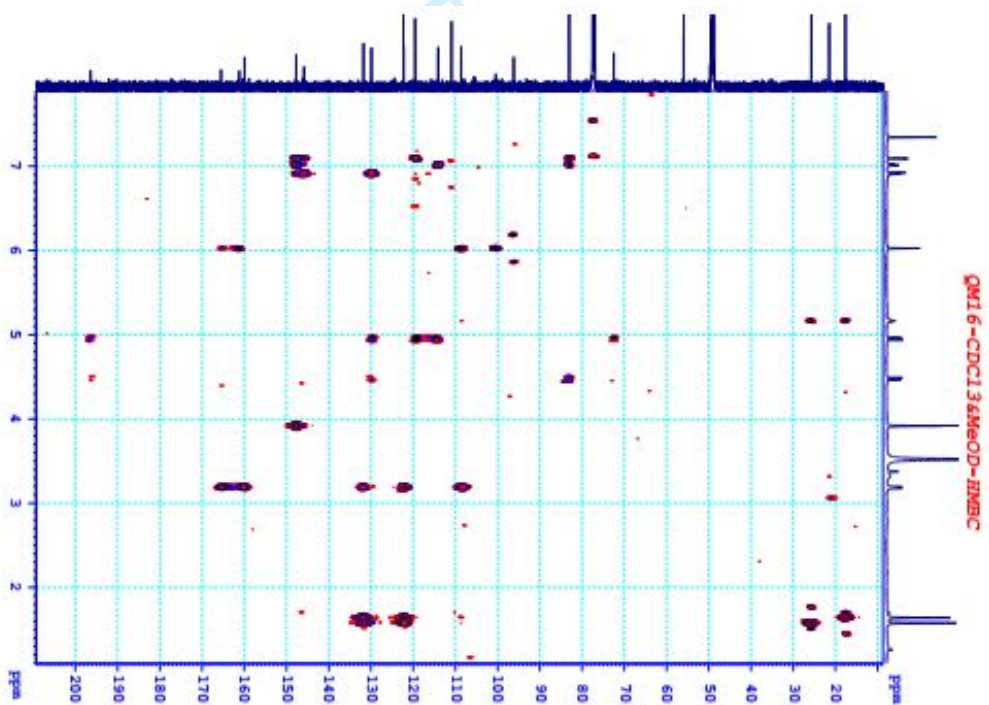


Figure S9. HMBC spectrum of compound 1

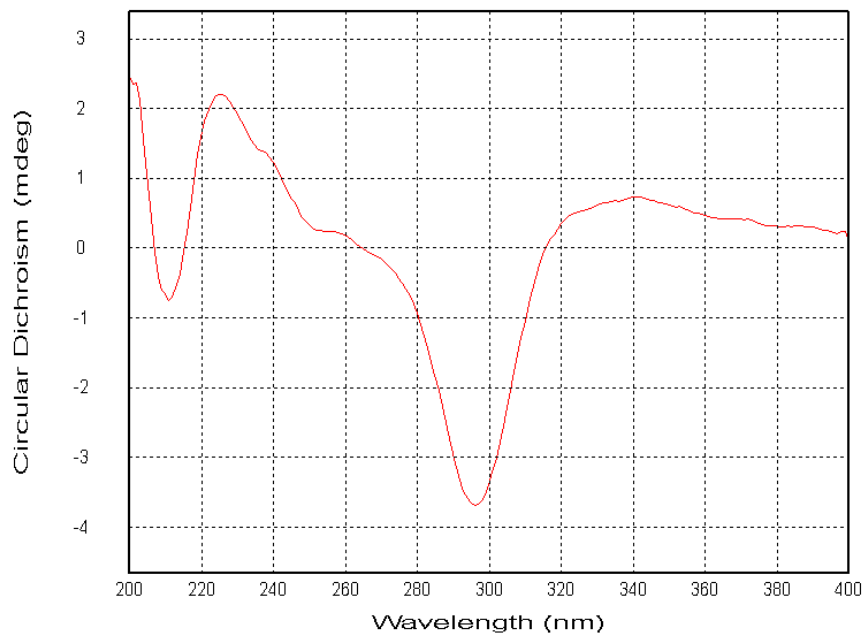


Figure S10. CD spectrum of compound 1

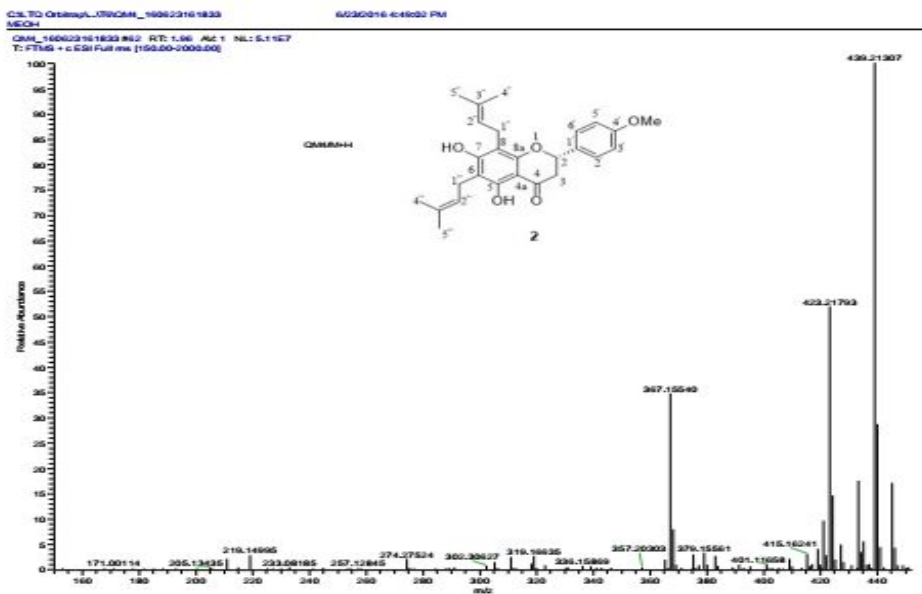


Figure S11. HR-MS spectrum of compound 2

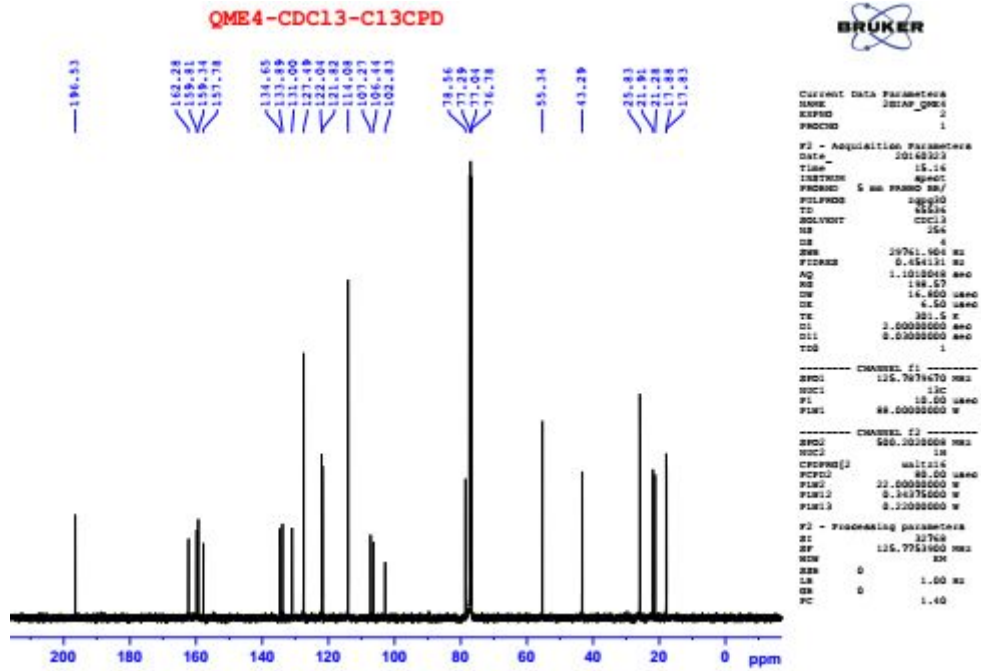


Figure S14. ¹³C-NMR spectrum of compound 2

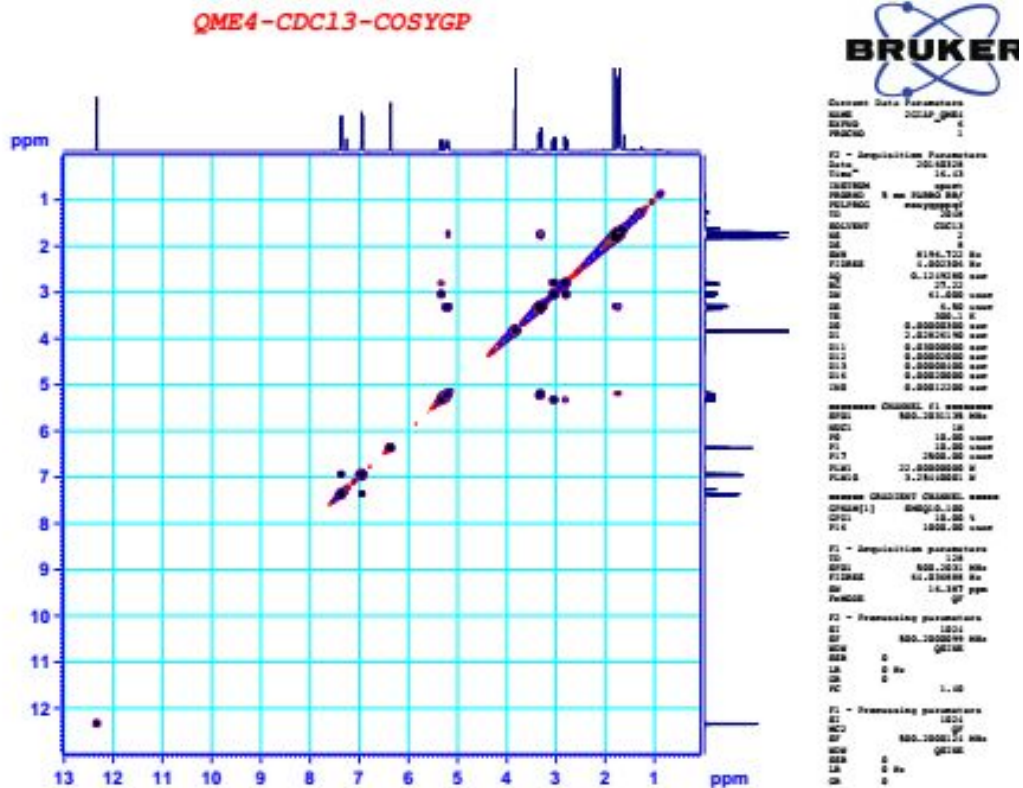


Figure S15. COSY spectrum of compound 2

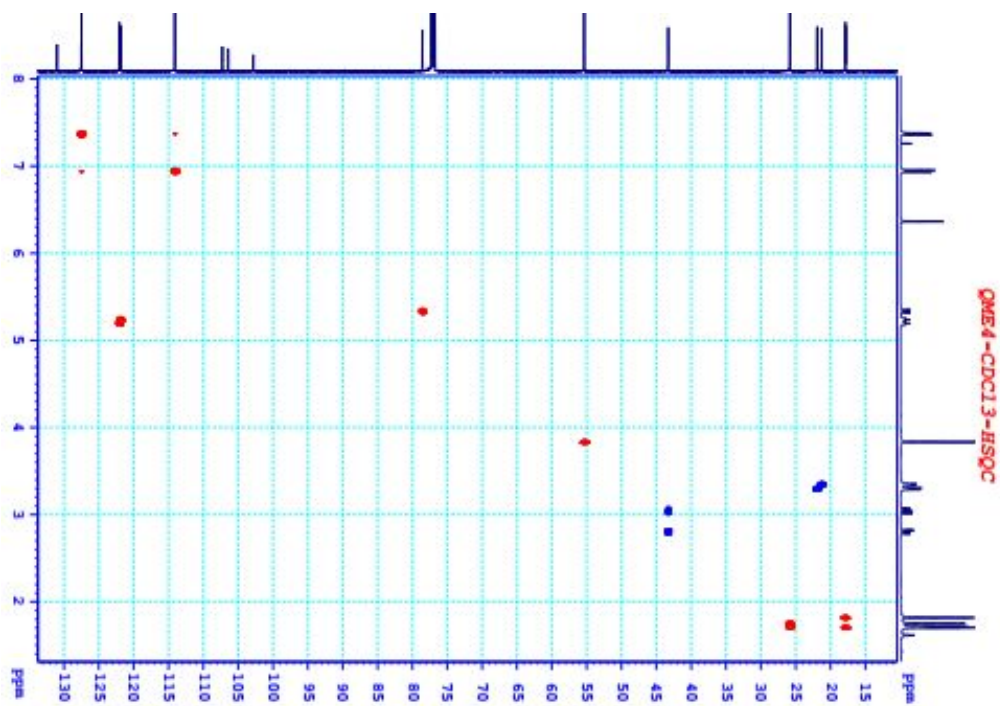


Figure S16. HSQC spectrum of compound 2

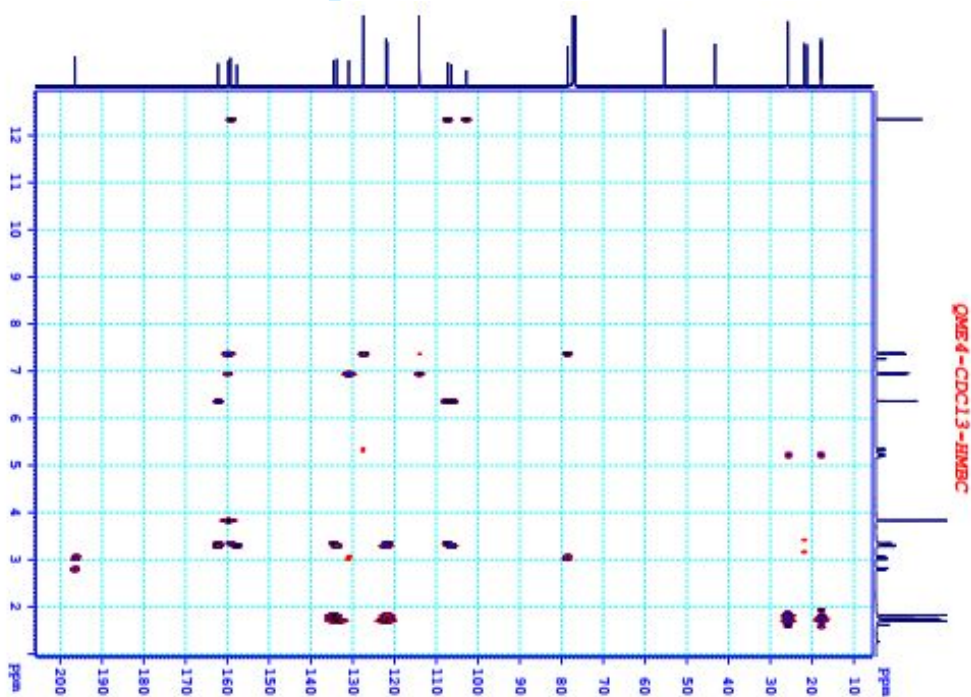
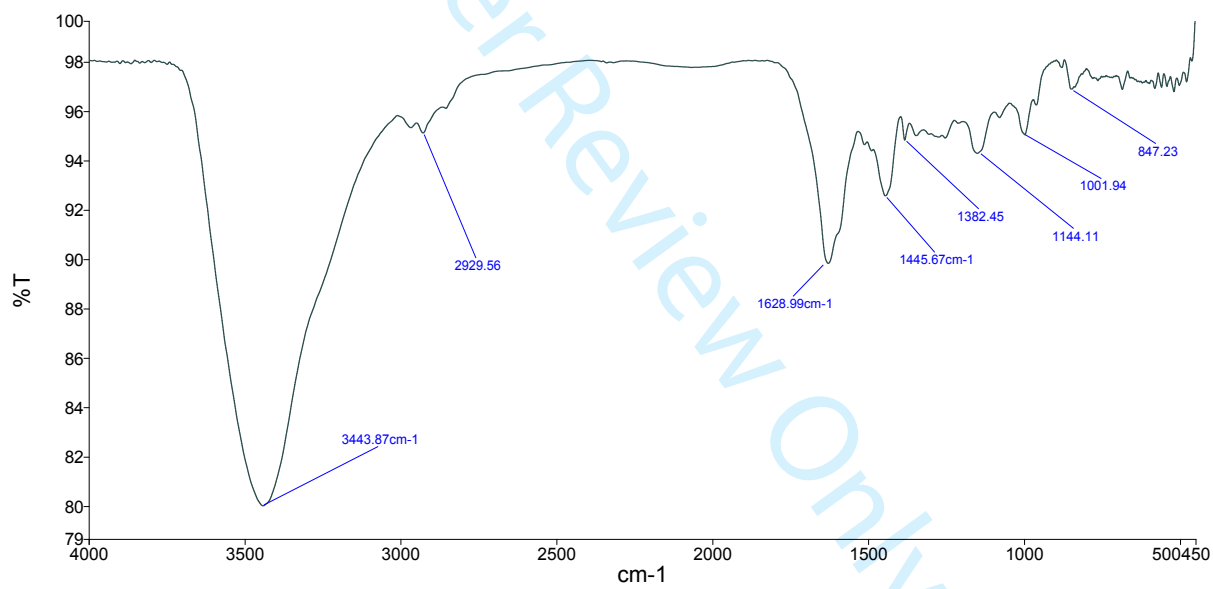
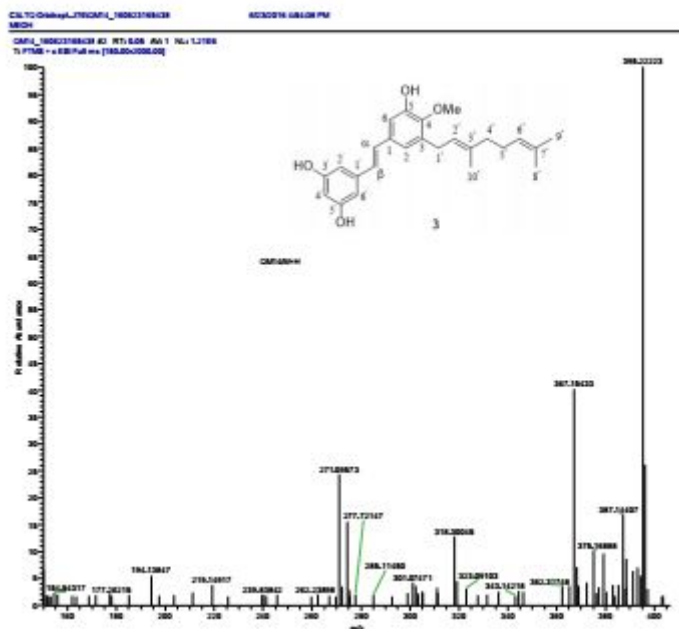


Figure S17. HMBC spectrum of compound 2

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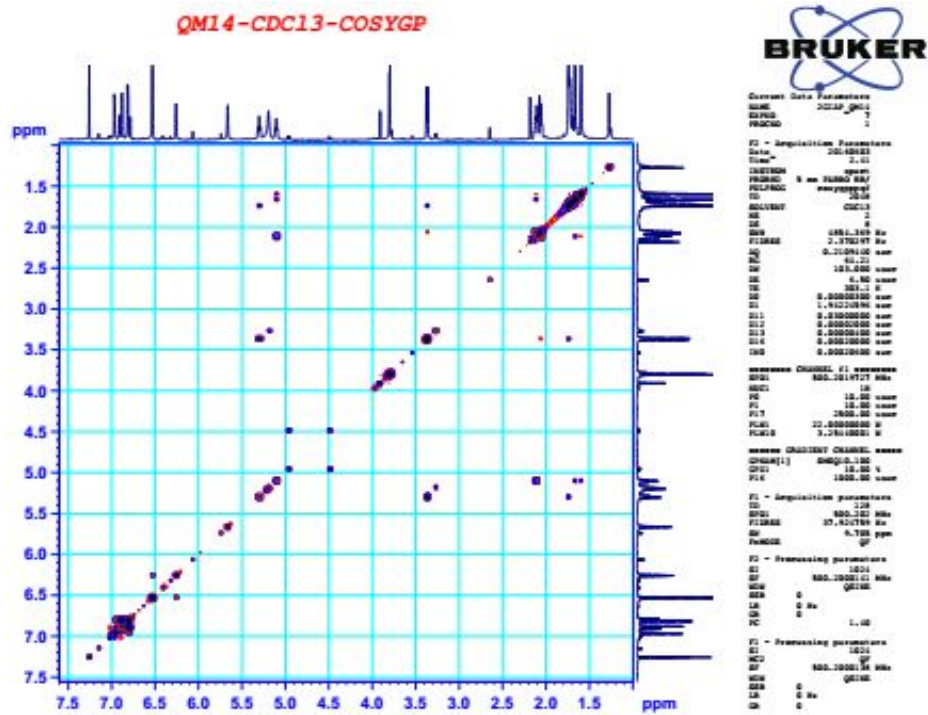


Figure S22. COSY spectrum of compound 3

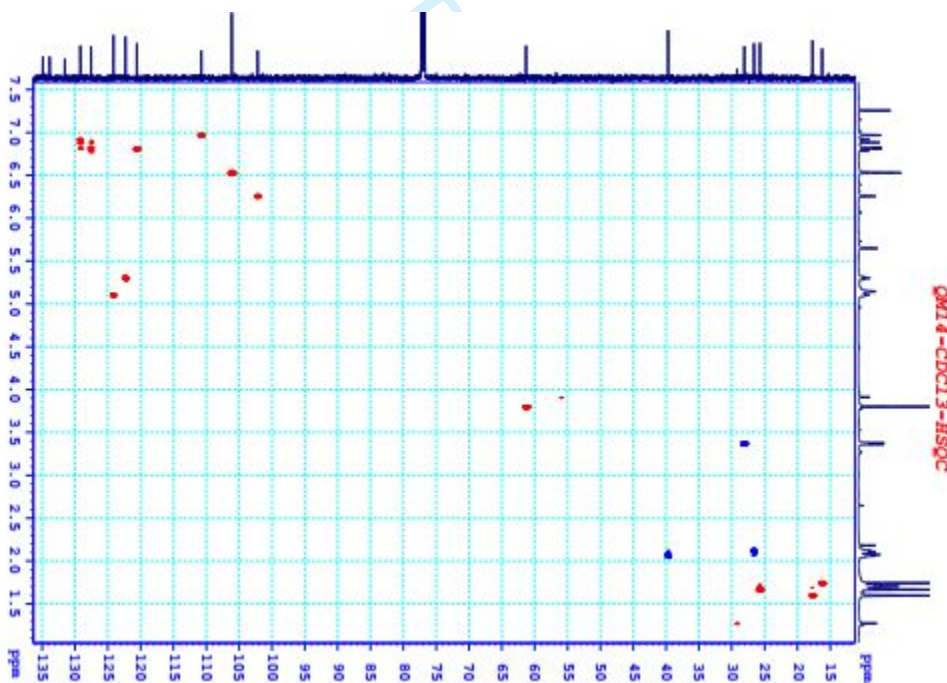


Figure S23. HSQC spectrum of compound 3

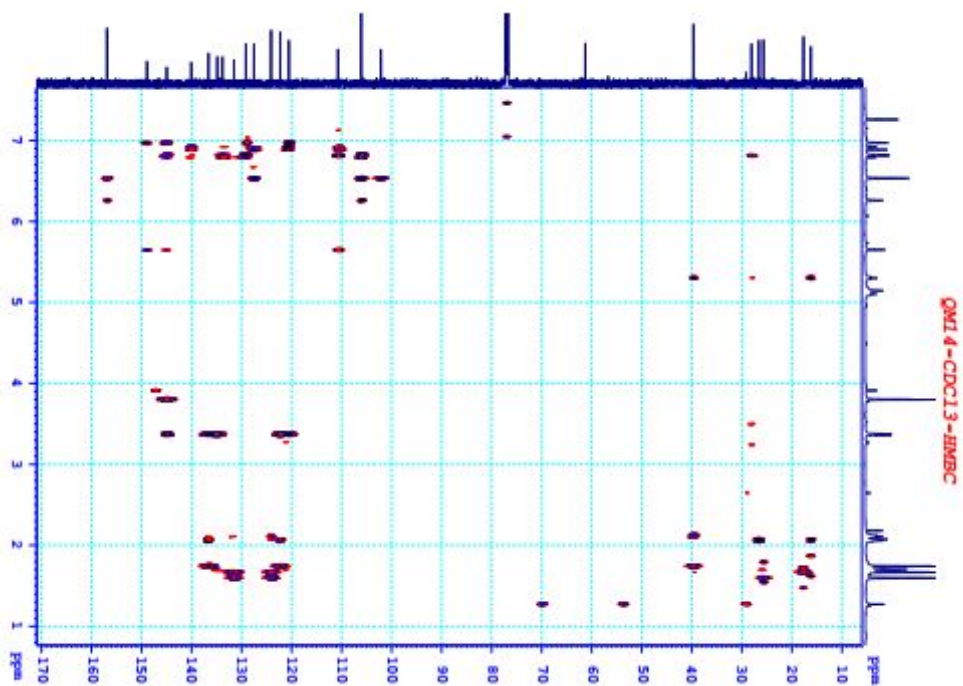


Figure S24. HMBC spectrum of compound 3