

# Cytotoxic Rocaglamide Derivatives from *Aglaia duppereana*

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Phytochemical investigation of *Aglaia duppereana* flowers led to the isolation of a new rocaglamide derivative and twelve known congeners. The structure of the new compound was unambiguously elucidated by spectroscopic techniques (1D- and 2D-NMR, HRESIMS). The isolated compounds exhibited a potent cytotoxic activity against mouse lymphoma (L5178Y) cells with EC<sub>50</sub> values ranging from 5.1 to 54.8 nM.

**Key words:** *Aglaia duppereana*, Rocaglamide, Cytotoxicity

## Introduction

The genus *Aglaia* represents the largest genus of the family Meliaceae and includes about 120 species mainly distributed in the tropical rainforest of Southeast Asia and on the Pacific islands (Pannell, 2007). Species of *Aglaia* form an important element of the humid tropical forests in the Indo-Malaysian region (Proksch *et al.*, 2001). Several species of *Aglaia* have long been used by native populations as heart stimulants and in the treatment of coughs, inflammation, diarrhea, and injuries (Proksch *et al.*, 2001).

Previous phytochemical studies of different *Aglaia* species established the occurrence of a class of characteristic compounds called flavaglines, which include rocaglamide, aglain, aglaforbesin, and forbagline derivatives (Ebada *et al.*, 2011). Only the rocaglamide derivatives, which feature a cyclopenta[*b*]benzofuran skeleton, exhibit interesting pharmacological properties including anticancer (Rivero-Cruz *et al.*, 2004; Kim *et al.*, 2006), anti-inflammatory (Proksch *et al.*, 2005), and insecticidal activities (Schneider *et al.*, 2000; Greger *et al.*, 2001). Additionally, rocaglamide derivatives are potent inhibitors of Raf-MEK-ERK (Polier

*et al.*, 2012) and of NF- $\kappa$ B (Baumann *et al.*, 2002). In this study, we report the isolation and identification of a new rocaglamide derivative together with twelve known ones from *A. duppereana* flowers, and on their cytotoxic activities.

## Results and Discussion

The methanolic extract of flowers of *Aglaia duppereana* was separated by column chromatography and preparative high-performance liquid chromatography (HPLC) to yield twelve known rocaglamide derivatives, **2–13**, in addition to the new compound **1** (Fig. 1). The molecular formula of compound **1**, C<sub>29</sub>H<sub>29</sub>NO<sub>9</sub>, was established from high-resolution-electrospray ionization-mass spectrometry (HRESIMS) (sodiated molecular ion peak [M + Na]<sup>+</sup> signal at *m/z* 558.1731; calcd. for C<sub>29</sub>H<sub>29</sub>NO<sub>9</sub>Na, 558.1735). Comparison of the <sup>1</sup>H and <sup>13</sup>C NMR spectra of **1** with those of previously isolated rocaglamides showed that compound **1** possesses a cyclopenta[*b*]benzofuran core which is characteristic for rocaglamides. The <sup>1</sup>H NMR spectrum (Table I) revealed the presence of three methoxy groups ( $\delta_{\text{H}}$  3.77, 3.79, and 3.86 ppm) and one acetoxy methyl group ( $\delta_{\text{H}}$  1.88 ppm).

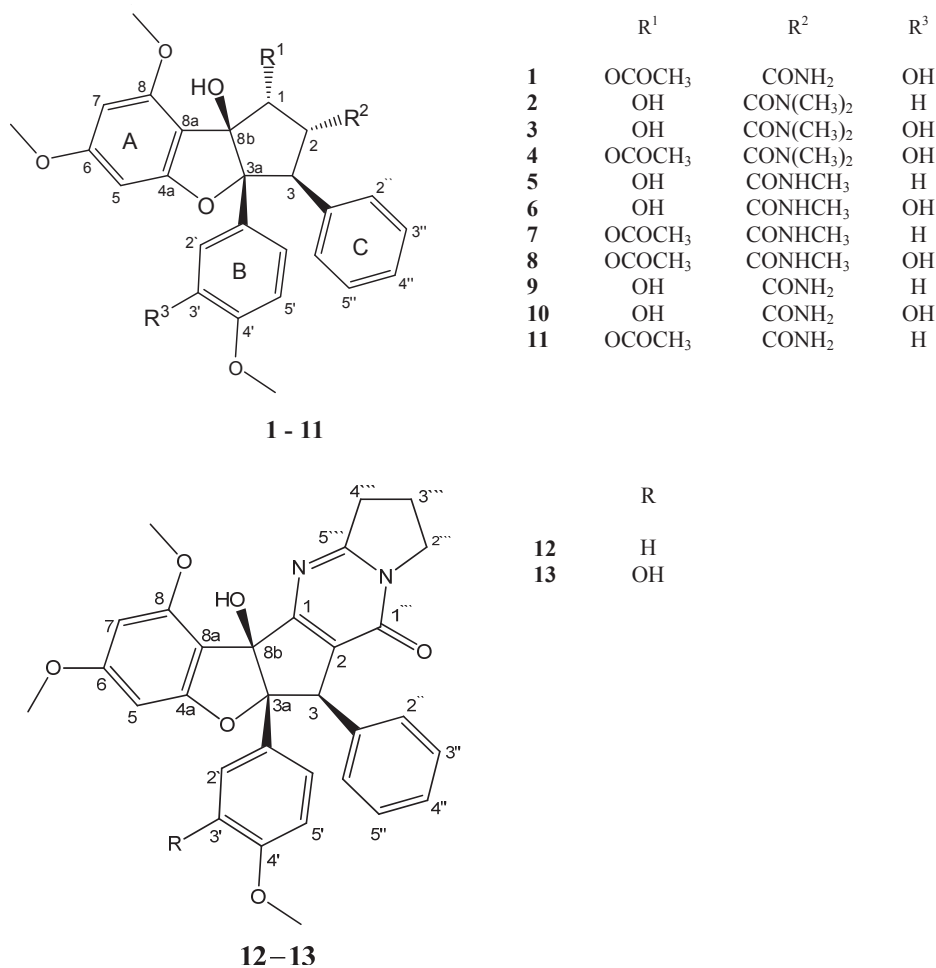


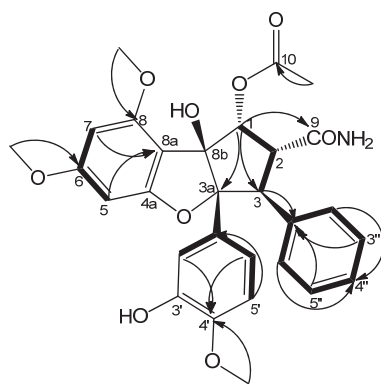
Fig. 1. Chemical structures of isolated compounds.

The aromatic region of the <sup>1</sup>H NMR spectrum of **1** displayed five proton resonances between δ<sub>H</sub> 7.03 ppm and δ<sub>H</sub> 7.07 ppm which were assigned to the monosubstituted aromatic ring C, whereas the ABX system of ring B was represented by two doublets protons at δ<sub>H</sub> 6.68 ppm (1H, *J* = 8.5 Hz) and δ<sub>H</sub> 6.83 ppm (1H, *J* = 2.2 Hz), and a doublet of doublets at δ<sub>H</sub> 6.79 ppm (1H, *J* = 2.2, 8.5 Hz). In addition, two signals of *meta*-coupled protons at δ<sub>H</sub> 6.16 ppm (1H, *J* = 1.9 Hz) and δ<sub>H</sub> 6.30 ppm (1H, *J* = 1.9 Hz) were assigned for ring A. Signals of the cyclopentane ring included two doublets at δ<sub>H</sub> 4.24 ppm (1H, *J* = 14.4 Hz) and δ<sub>H</sub> 6.12 ppm (1H, *J* = 5.8 Hz), and a doublet of doublets at δ<sub>H</sub> 4.07 ppm (1H, *J* = 5.8, 14.4 Hz). Structural elucidation was further achieved through the <sup>1</sup>H-<sup>1</sup>H

COSY spectrum (Fig. 2) showing four spin systems, CH(1)CH(2)CH(3), CH(5)CH(7), CH(5'')-CH(6'')CH(2''), and CH(2'')CH(3'')CH(4'')CH(5'')CH(6''). The assignment was further supported by inspection of the HMBC spectrum (Fig. 2) which showed correlations from OCH<sub>3</sub>-4' (δ<sub>H</sub> 3.77 ppm) to C-4' (δ<sub>C</sub> 148.0 ppm), OCH<sub>3</sub>-6 (δ<sub>H</sub> 3.86 ppm) to C-6 (δ<sub>C</sub> 166.0 ppm), OCH<sub>3</sub>-8 (δ<sub>H</sub> 3.79 ppm) to C-8 (δ<sub>C</sub> 160.0 ppm), and CH<sub>3</sub>-10 (δ<sub>H</sub> 1.88 ppm) to C-10 (δ<sub>C</sub> 171.8 ppm). In addition, the HMBC spectrum of **1** (Fig. 2) showed long-range correlations from H-1 (δ<sub>H</sub> 6.12 ppm) to C-3 (δ<sub>C</sub> 57.0 ppm), C-3a (δ<sub>C</sub> 102.0 ppm), C-8b (δ<sub>C</sub> 94.0 ppm), and C-10 (δ<sub>C</sub> 171.8 ppm), and from H-2 (δ<sub>H</sub> 4.07 ppm) to C-3 (δ<sub>C</sub> 57.0 ppm) and C-9 (δ<sub>C</sub> 174.0 ppm). Based on the aforementioned 1D

Table I. NMR data [at 600 ( $^1\text{H}$ ) and 150 ( $^{13}\text{C}$ ) MHz in  $\text{MeOH-}d_4$ ] of the new rocaglamide derivative **1**.

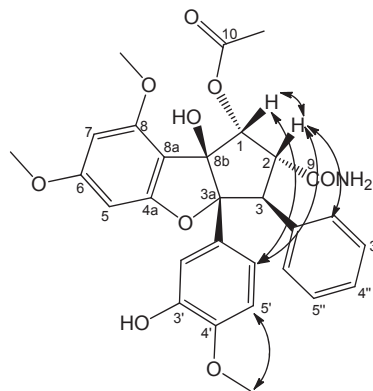
Position	$\delta_{\text{H}}$	$\delta_{\text{C}}$	HMBC (H to C)
1	6.12 (1H, d, $J = 5.8$ Hz)	81.0	3, 3a, 8b, 9, 10
2	4.07 (1H, dd, $J = 5.8, 14.4$ Hz)	51.0	3, 9
3	4.24 (1H, d, $J = 14.4$ Hz)	57.0	2, 3a, 9, 1', 1'', 2''/6''
3a		102.0	
4a		161.9	
5	6.30 (1H, d, $J = 1.9$ Hz)	89.0	6, 4a, 7, 8a
6		166.0	
7	6.16 (1H, d, $J = 1.9$ Hz)	92.5	5, 6, 8, 8a
8		160.0	
8a		108.0	
8b		94.0	
9		174.0	
10		171.8	
1'		130.0	
2'	6.83 (1H, d, $J = 2.2$ Hz)	116.4	3', 4', 6', 3a
3'		146.0	
4'		148.0	
5'	6.68 (1H, d, $J = 8.5$ Hz)	111.0	1', 3', 4'
6'	6.79 (1H, dd, $J = 2.2, 8.5$ Hz)	121.8	2', 4'
1''		138.5	
2''/6''	7.03 (2H, m)	128.5	3'', 4'', 5'', 2''/6''
3''/5''	7.07 (3H, m)	127.8	1'', 2'', 4'', 6'', 3''/5''
4''		127.0	2'', 3'', 5'', 6''
OMe-4'	3.77 (3H, s)	56.1	4'
OMe-6	3.86 (3H, s)	56.0	6
OMe-8	3.79 (3H, s)	55.7	8
-OCOMe	1.88 (3H, s)	21.5	10

Fig. 2. COSY and key-HMBC correlations of compound **1**.

and 2D spectral data, compound **1** was identified as a new rocaglamide derivative possessing three methoxy groups at C-6, C-8, and C-4'; two hydroxy groups at C-3' and C-8b; one acetoxy group at C-1; and one carboxamide moiety at C-2. Structurally, compound **1** resembled the known C-1-*O*-

acetyl-3'-hydroxyrocaglamide (**4**) (Nugroho *et al.*, 1997) albeit lacking its two *N*-methyl groups.

The relative stereochemistry of **1** was deduced by a ROESY experiment (Fig. 3). The proton signal of H-1 ( $\delta_{\text{H}}$  6.12 ppm) showed a clear ROESY correlation with H-2 ( $\delta_{\text{H}}$  4.07 ppm). Moreover, H-2 ( $\delta_{\text{H}}$  4.07 ppm) showed ROESY

Fig. 3. Key-ROESY correlations of compound **1**.

correlations to H-6' ( $\delta_{\text{H}}$  6.79 ppm) and H-2''. In addition, the vicinal coupling constants  $J_{1,2}$  and  $J_{2,3}$  of compound **1** (Table I) which are very similar to those of rocaglamide (**2**), a compound also isolated in this study, hinted at the same relative configuration of C-1 and C-2 compared to C-3, C-3a, and C-8b. Thus, the deduced stereochemistry of **1** was the same as the relative configuration of other naturally occurring rocaglamide derivatives. Compound **1** was isolated from the same source as other known rocaglamides, whose absolute configurations were well-established through synthesis (King *et al.*, 1982; Trost *et al.*, 1990). The optical rotation of **1** was  $[\alpha]_{\text{D}}^{20} -85.1^{\circ}$  (*c* 0.54,  $\text{CHCl}_3$ ), very similar to that reported for the synthetic product rocaglamide,  $[\alpha]_{\text{D}}^{20} -88.8^{\circ}$  (*c* 1.03,  $\text{CHCl}_3$ ), and previously isolated rocaglamide (**2**),  $[\alpha]_{\text{D}}^{20} -93.0^{\circ}$  (*c* 1.88,  $\text{CHCl}_3$ ) (King *et al.*, 1982; Trost *et al.*, 1990). In conclusion, compound **1** was deduced to have the same absolute configuration at the stereocenters C-1, C-2, C-3, C-3a, and C-8b (Fig. 3) as other known rocaglamide derivatives. Thus, **1** was elucidated as C-1-*O*-acetyl-3'-hydroxydidesmethylrocaglamide.

Based on the spectral data and by comparison with those of the literature, the twelve known compounds (Fig. 1) were identified as rocaglamide (**2**) (King *et al.*, 1982; Nugroho *et al.*, 1997), C-3'-hydroxyrocaglamide (**3**) (Nugroho *et al.*, 1997), C-1-*O*-acetyl-3'-hydroxyrocaglamide (**4**) (Nugroho *et al.*, 1997), desmethylrocaglamide (**5**) (Ishibashi *et al.*, 1993), C-3'-hydroxydesmethylrocaglamide (**6**) (Nugroho *et al.*, 1999), C-1-*O*-acetyl-desmethylrocaglamide (**7**) (Hiort *et al.*, 1999), C-1-*O*-acetyl-3'-hydroxydesmethylrocaglamide (**8**) (Güssregen *et al.*, 1997), didesmethylrocaglamide (**9**) (Dumontet *et al.*, 1996), C-3'-hydroxydidesmethylrocaglamide (**10**) (Güssregen *et al.*, 1997), C-1-*O*-acetyldidesmethylrocaglamide (**11**) (Chaidir *et al.*, 1999), dehydroaglaiastatin (**12**) (Kokpol *et al.*, 1994), and C-3'-hydroxydidehydroaglaiastatin (**13**) (Chaidir *et al.*, 1999).

All isolated compounds were subjected to a cytotoxicity assay employing the murine lymphoma L5178Y cell line, the results of which are summarized in Table II. All isolated compounds exhibited a potent cytotoxic activity against the mouse lymphoma cells with  $\text{EC}_{50}$  values ranging from 5.1 to 54.8 nM.

Table II.  $\text{EC}_{50}$  values of the isolated compounds against the L5178Y mouse lymphoma cell line.

Compound	$\text{EC}_{50} \pm \text{SD}$ [nM]
<b>1</b>	21.9 $\pm$ 0.01
<b>2</b>	47.5 $\pm$ 0.02
<b>3</b>	13.4 $\pm$ 0.01
<b>4</b>	17.8 $\pm$ 0.03
<b>5</b>	5.1 $\pm$ 0.01
<b>6</b>	27.4 $\pm$ 0.08
<b>7</b>	12.2 $\pm$ 0.03
<b>8</b>	10.0 $\pm$ 0.02
<b>9</b>	13.6 $\pm$ 0.02
<b>10</b>	54.8 $\pm$ 0.03
<b>11</b>	13.5 $\pm$ 0.09
<b>12</b>	5.7 $\pm$ 0.08
<b>13</b>	29.6 $\pm$ 0.03
Kahalalide F (positive control)	(4.3 $\pm$ 0.04) $\mu\text{M}$

## Experimental

### Plant material

Flowers of *Aglaia duppereana* were collected near Hanoi, Vietnam, in 2011. A voucher specimen is kept in the Institute of Pharmaceutical Biology and Biotechnology, Heinrich-Heine-University, Duesseldorf, Germany.

### General experimental procedures

Vacuum liquid chromatography (VLC) was performed on silica gel 60 (0.040–0.063 mm; Merck, Darmstadt, Germany). Column chromatography (CC) was carried out on silica gel 60 (Merck) and Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Uppsala, Sweden). For analytical HPLC, samples were injected into a HPLC system (Dionex, Munich, Germany) equipped with a photodiode array detector (Dionex). Routine detection was at 235, 254, 280, and 340 nm. The separation column (125 mm x 4 mm ID) was prefilled with eurosphere 100-5 C-18, 5 $\mu\text{m}$  (Knauer, Berlin, Germany). Separation was achieved by applying a linear gradient from 90%  $\text{H}_2\text{O}$  (adjusted to pH 2.0 by addition of formic acid) to 100% MeOH over 40 min. TLC analysis was carried out using aluminium sheets precoated with silica gel 60 F<sub>254</sub> (Merck). Preparative HPLC separations were done on a LaChrom-Merck (Hitachi, Darmstadt, Germany) HPLC machine, equipped with an L-7100 pump, L-7400 UV detector, and a 0-18 column (Knauer; 300 mm x 8 mm ID; prefilled with eurosphere 100-10 C-18; flow rate, 5 mL/

min; UV detection, at 280 nm). For preparative HPLC separations, the solvent system consisted of MeOH, or acetonitrile and nanopure H<sub>2</sub>O that had been acidified with 0.1% formic acid. ESI mass spectra were obtained on a ThermoFinnigan (Finnigan Mat GmbH, Bremen, Germany) LCQ DECA mass spectrometer coupled to an Agilent (Agilent Technologies Deutschland GmbH & Co. KG, Waldbronn, Germany) 1100 HPLC system equipped with a photodiode array detector. HRESI mass spectra were recorded on a LTQ FT-MS-Orbitrap instrument (Finnigan Mat). 1D- and 2D-NMR spectra were recorded at 300 K on either a Bruker (Daltonics, Bremen, Germany) ARX-500 or AVANCE DMX-600 NMR spectrometer (Bruker Biospin, Rheinstetten, Germany). Samples were dissolved in different deuterated solvents, the choice of which was dependent on the solubility of each sample.

#### Extraction and isolation

Air-dried flowers (1 kg) were ground and exhaustively extracted with MeOH at room temperature. Following the evaporation of the solvent, the extract was defatted with *n*-hexane. The defatted MeOH extract was then chromatographed over silica gel F<sub>254</sub> (Merck) using gradient elution [*n*-hexane/EtOAc (100:0 to 0:100 v/v) then dichloromethane (DCM)/MeOH (100:0 to 0:100 v/v)]. Further purification was achieved through repeated chromatographic separation using silica gel (Merck) [mobile phase: CH<sub>2</sub>Cl<sub>2</sub>/isoPrOH (9:1 v/v)], size exclusion chromatography over Sephadex LH-20 (Merck L7100) [mobile phase: MeOH and DCM/MeOH (1:1 v/v)], and diol (Merck) [mobile phase: *n*-hexane/acetone (7:3 v/v) and DCM/MeOH (9.5:0.5–7:3 v/v)]. Final purification

was done using preparative HPLC over RP-18 columns (Merck) (mobile phase: mixtures of MeOH and H<sub>2</sub>O, and acetonitrile with H<sub>2</sub>O). Fractions were monitored by TLC on silica gel F<sub>254</sub> (Merck) [mobile phase: CH<sub>2</sub>Cl<sub>2</sub>/isoPrOH (9:1 v/v)]. Yields were: **1**, 2.3 mg; **2**, 1.9 mg; **3**, 0.8 mg; **4**, 11.4 mg; **5**, 4.5 mg; **6**, 0.7 mg; **7**, 5.2 mg; **8**, 5.0 mg; **9**, 0.7 mg; **10**, 1.0 mg; **11**, 2.0 mg; **12**, 4.1 mg; and **13**, 16.0 mg.

*C-1-O-Acetyl-3'-hydroxydidesmethylrocaglamide* (rocaglamide MW, **1**): White amorphous solid. – [ $\alpha$ ]<sub>D</sub><sup>20</sup> –85.1° (c 0.54, CHCl<sub>3</sub>). – UV:  $\lambda_{\max}$  (PDA) = 206.9, 278 nm. – <sup>1</sup>H and <sup>13</sup>C NMR (MeOH-*d*<sub>4</sub>): see Table I. – ESIMS positive: *m/z* = 535.9 [M + H]<sup>+</sup>; negative: *m/z* = 534.3 [M – H]<sup>–</sup>. – HRESIMS: *m/z* = 558.1731 [M + Na]<sup>+</sup> (calcd. for C<sub>29</sub>H<sub>29</sub>NO<sub>9</sub>Na, 558.1735).

#### Cell proliferation assay

Cytotoxicity was tested against the L5178Y mouse lymphoma cell line using the microculture 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Ashour *et al.*, 2006; Carmichael *et al.*, 1987). Experiments were repeated three times and carried out in triplicate. As negative controls, media with 0.1% (v/v) EtOH were included in all experiments. The depsipeptide kahalalide F isolated from *Elysia grandifolia* was used as positive control (Ashour *et al.*, 2006). The EC<sub>50</sub> value is defined as the half maximal effective concentration of each isolated compound and expressed in nM.

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Ashour M., Edrada-Ebel R. A., Ebel R., Wray V., Waetjen W., Padmakumar K., Mueller W. E. G., Lin W., and Proksch P. (2006), Kahalalide derivatives from the Indian sacoglossan mollusk *Elysia grandifolia*. *J. Nat. Prod.* **69**, 1547–1553.  
Baumann B., Bohnenstengel F., Siegmund D., Wajant H., Weber C., Herr I., Debatin K. M., Proksch P., and Wirth T. (2002), Rocaglamide derivatives are potent inhibitor of NF- $\kappa$ B activation in T-cell. *J. Biol. Chem.* **277**, 44791–44800.

Carmichael J., DeGraff W. G., Gazdar A. F., Minna J. D., and Mitchell J. B. (1987), Evaluation of a tetrazolium-based semiautomated colorimetric assay: Assessment of radiosensitivity. *Cancer Res.* **47**, 943–946.  
Chaidir H. J., Nugroho B. W., Bohnenstengel F. I., Wray V., Witte L., Hung P. D., Kiet L. C., Sumaryono W., and Proksch P. (1999), New insecticidal rocaglamide derivatives from flowers of *Aglaia duppereana* (Meliaceae). *Phytochemistry* **52**, 837–842.

- Dumontet V., Thoison O., Omobuwajo O. R., Martin M.-T., Perromat G., Chiaroni A., Riche C., País M., and Sévenet T. (1996), New nitrogenous and aromatic derivatives from *Aglaia argentea* and *A. forbesii*. *Tetrahedron* **52**, 6931–6942.
- Ebada S. S., Lajkiewicz N., Porco J. A., Li-Weber M., and Proksch P. (2011), Chemistry and biology of rocaglamides (= flavaglines) and related derivatives from *Aglaia* species (Meliaceae). *Prog. Chem. Org. Nat. Prod.* **94**, 1–58.
- Greger H., Pache T., Brem B., Bacher M., and Hofer O. (2001), Insecticidal flavaglines and other compounds from Fijian *Aglaia* species. *Phytochemistry* **57**, 57–64.
- Güssregen B., Fuhr M., Nugroho B. W., Wray V., Witte L., and Proksch P. (1997), New insecticidal rocaglamide derivatives from flowers of *Aglaia odorata*. *Z. Naturforsch.* **52c**, 339–344.
- Hiort J. C., Bohnenstengel F. I., Nugroho B. W., Schneider C., Wray V., Witte L., Hung P. D., Kiet L. C., and Proksch P. (1999), New insecticidal rocaglamide derivatives from the roots of *Aglaia duppereana*. *J. Nat. Prod.* **62**, 1632–1635.
- Ishibashi F., Satasook C., Isman M. B., and Towers G. H. N. (1993), Insecticidal 1*H*-cyclopentatetrahydro[*b*]benzofurans from *Aglaia odorata*. *Phytochemistry* **32**, 307–310.
- Kim S., Salim A. A., Swanson S. M., and Kinghorn A. D. (2006), Potential of cyclopenta[*b*]benzofurans from *Aglaia* species in cancer chemotherapy. *Anticancer Agents Med. Chem.* **6**, 319–345.
- King M. L., Chiang C. C., Ling H. C., Fujita E., Ochiai M., and McPhail A. T. (1982), X-ray crystal structure of rocaglamide, a novel antileukemic 1*H*-cyclopenta[*b*]benzofuran from *Aglaia elliptifolia*. *J. Chem. Soc., Chem. Commun.* **20**, 1150–1151.
- Kokpol U., Venaskulchai B., Simpson J., and Weavers R. T. (1994), Isolation and X-ray structure determination of a novel pyrimidinone from *Aglaia odorata*. *J. Chem. Soc., Chem. Commun.* **6**, 773–774.
- Nugroho B. W., Edrada R. A., Güssregen B., Wray V., Witte L., and Proksch P. (1997), Insecticidal rocaglamide derivatives from *Aglaia duppereana*. *Phytochemistry* **44**, 1455–1461.
- Nugroho B. W., Edrada R. A., Wray V., Witte L., Bringmann G., Gehling M., and Proksch P. (1999), An insecticidal rocaglamide derivative and related compounds from *Aglaia odorata* (Meliaceae). *Phytochemistry* **51**, 367–376.
- Pannell C. M. (2007), *Aglaia*. In: *Tree Flora of Sabah and Sarawak* (Soepadmo E., Saw L. G., Chung R. C. K., and Kiew R., eds.). Ampang Press Sdn Bhd, Kuala Lumpur, Malaysia, p. 24.
- Polier G., Neumann J., Thuaud F., Ribeiro N., Gelhaus C., Schmidt H., Giaisi M., Köhler R., Mueller W. W., Proksch P., Leippe M., Janssen O., Desaubry L., Krammer P. H., and Li-Weber M. (2012), The natural anticancer compounds rocaglamides inhibit the Raf-MEK-ERK pathway by targeting prohibitin 1 and 2. *Chem. Biol.* **19**, 1093–1104.
- Proksch P., Edrada R. A., Ebel R., Bohnenstengel F. I., and Nugroho B. W. (2001), Chemistry and biological activity of rocaglamide derivatives and related compounds in *Aglaia* species (Meliaceae). *Curr. Org. Chem.* **5**, 923–938.
- Proksch P., Giaisi M., Treiber M. K., Palfi K., Merling A., Spring H., Krammer P. H., and Li-Weber M. (2005), Rocaglamide derivatives are immunosuppressive phytochemicals that target NF-AT activity in T cells. *J. Immunol.* **174**, 7075–7084.
- Rivero-Cruz J. F., Chai H. B., Kardono L. B., Setyowati F. M., Afriatini J. J., Riswan S., Farnsworth N. R., Cordell G. A., Pezzuto J. M., Swanson S. M., and Kinghorn A. D. (2004), Cytotoxic constituents of the twigs and leaves of *Aglaia rubiginosa*. *J. Nat. Prod.* **67**, 343–347.
- Schneider C., Bohnenstengel F. I., Nugroho B. W., Wray V., Witte L., Hung P. D., Kiet L. C., and Proksch P. (2000), Insecticidal rocaglamide derivatives from *Aglaia spectabilis* (Meliaceae). *Phytochemistry* **54**, 731–736.
- Trost B. M., Greenspan P. D., Yang B. V., and Sauliner M. G. (1990), An unusual oxidative cyclization. A synthesis and absolute stereochemical assignment of (–)-rocaglamide. *J. Am. Chem. Soc.* **112**, 9022–9024.