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New bisamide compounds from the bark of *Aglaia eximia* (Meliaceae)

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ABSTRACT

Two new bisamide compounds, eximiamide A (**1**) and eximiamide B (**2**) were isolated from the bark of *Aglaia eximia* (Meliaceae). The chemical structures of the new compound were elucidated on the basis of spectroscopic data. All of the compounds were evaluated for their cytotoxic effects against P-388 murine leukemia cells. Compounds **1** and **2** exhibited cytotoxic activity against P-388 murine leukemia cells with IC_{50} values of 7.6 and 8.5 μg/mL, respectively.

1. Introduction

The genus *Aglaia* (Meliaceae) comprises more than 100 species and mainly distributed in tropical and subtropical regions (Pannell, 1992; Inada et al., 2001). Previous phytochemical studies of *Aglaia* genus have revealed the presence of a variety of compounds with interesting biological activities including several rocaglate derivatives (Wu et al., 1997; Kim et al., 2005; Su et al., 2006 Chaidir et al., 1999), bisamides (Saifah et al., 1999; Duong et al., 2007), triterpenoids (Harneti et al., 2012 Xie et al., 2007), steroids (Awang et al., 2012; Harneti et al., 2014), limonoids (Fuzzati et al., 1996), sesquiterpenes (Joycharat et al., 2010), lignans (Wang et al., 2002, 2004) and flavonoids (Nugroho et al., 1999).

Recently, several bisamide derived from putrescine, has been found from this genus (Chin et al., 2010). Among these bisamides, a group of compounds found in several *Aglaia* species have been reported as exhibiting cytotoxic activity (Kim et al., 2006). As part of our continuing search for anticancer candidate compounds from *Aglaia eximia*, we isolated and described a new stigmastane steroid, 3,4-epoxy-(22*R*,25)-tetrahydrofuran-stigmast-5-en from the bark of *A. eximia* (Harneti et al., 2014). In the further screening for cytotoxic compounds from polar fraction of *A. eximia*, we found that the methanol extract of the bark of *A. eximia* exhibited a cytotoxic activity against P-388 murine leukimia cells with an IC_{50} of 40 μg/mL. We report herein the isolation and structure elucidation of two new bisamide compounds, eximiamide A (**1**) and eximiamide B (**2**), together with their cytotoxic activity against P-388 murine leukimia cells.

2. Results and discussion

Bark of *A. eximia* were grounded and successively extracted with *n*-hexane, ethyl acetate and methanol at room temperature. The methanol extract was chromatographed over a vacuum-liquid chromatographed (VLC) column packed with silica gel 60 by gradient elution. The VLC fractions were repeatedly subjected to normal and reverse-phase column chromatography and preparative TLC on silica gel GF_{254} to afford two cytotoxic compounds **1**–**2** (Fig. 1).

Compound **1** was obtained as yellow oil, $[\alpha]_{20}^{D}$ −10.5 (*c*, 0.1, MeOH), the molecular formula of **1** was established to be $C_{27}H_{52}N_6O_{11}$ from HR-TOFMS spectrum which showed a $[M-H]^+$ pseudo molecular ion peak *m*/*z* 637.7206 (calcd. for $C_{27}H_{52}N_6O_{11}$ *m*/*z* 636.7354), together with NMR data (Table 1), thus requiring five degree of unsaturation. The UV spectrum showed absorption peak at λ_{max} nm (log ε): 262 (5.25), suggesting the presence of an α,β-unsaturated ketone group. The IR spectrum showed absorption peaks due to hydroxyl (3400 cm^{-1}), NH asymmetric (2935 cm^{-1}), amide carbonyl (1681 cm^{-1}), NH bending

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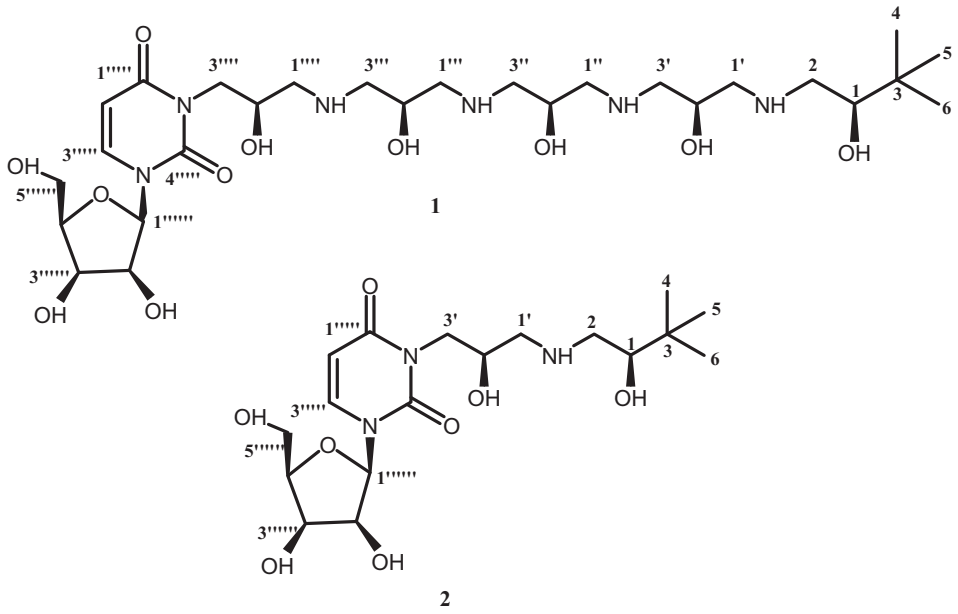

Fig. 1. Structures of Compounds **1**–**2**.

Table 1
NMR data (500 MHz for ^{1}H and 125 MHz for ^{13}C in CD_3OD) for **1** and **2**.

Position	1		2	
	^{13}C NMR δ_C (mult.)	^{1}H NMR δ_H (integral, mult., J Hz)	^{13}C NMR δ_C (mult.)	^{1}H NMR δ_H (integral, mult., J Hz)
1	75.9 (d)	4.14 (1H, t, 4.5)	72.5 (d)	4.14 (1H, t, 4.5)
2	64.5 (t)	3.49 (1H, d, 6.5)	63.0 (t)	3.50 (1H, d, 4.8)
		3.60 (1H, d, 5.2)		3.54 (1H, d, 5.8)
3	38.7 (s)	–	37.5 (s)	–
4	30.8 (q)	2.16 (3H, s)	29.5 (q)	1.86 (3H, s)
5	30.8 (q)	2.16 (3H, s)	29.5 (q)	1.86 (3H, s)
6	30.8 (q)	2.16 (3H, s)	29.5 (q)	1.86 (3H, s)
1′	64.5 (t)	3.52 (1H, d, 5.9)	63.0 (t)	3.50 (1H, d, 4.8)
		3.57 (1H, d, 5.2)		3.54 (1H, d, 5.8)
2′	73.9 (d)	3.65 (1H, q, 5.2, 11.0)	74.4 (d)	3.62 (1H, q, 5.8, 10.5)
3′	64.5 (t)	3.52 (1H, d, 5.9)	63.0 (t)	3.46 (1H, d, 6.0)
		3.57 (1H, d, 5.2)		3.56 (1H, d, 4.7)
1″	64.5 (t)	3.52 (1H, d, 5.9)		
		3.57 (1H, d, 5.2)		
2″	73.9 (d)	3.65 (1H, q, 5.2, 11.0)		
3″	64.5 (t)	3.52 (1H, d, 5.9)		
		3.57 (1H, d, 5.2)		
1‴	64.5 (t)	3.52 (1H, d, 5.9)		
		3.57 (1H, d, 5.2)		
2‴	73.9 (d)	3.65 (1H, q, 5.2, 11.0)		
3‴	64.5 (t)	3.52 (1H, d, 5.9)		
		3.57 (1H, d, 5.2)		
1⁗	64.5 (t)	3.52 (1H, d, 5.9)		
		3.57 (1H, d, 5.2)		
2⁗	73.9 (d)	3.65 (1H, q, 5.2, 11.0)		
3⁗	64.5 (t)	3.49 (1H, d, 6.5)		
		3.60 (1H, d, 5.2)		
1⁗′	166.3 (s)	–	165.4 (s)	–
2⁗′	102.7(d)	5.69 (1H, d, 8.4)	101.3 (d)	5.66 (1H, d, 8.0)
3⁗′	142.8 (d)	8,01 (1H, d, 8.4)	141.3 (d)	7.97(1H, d, 8.0)
4⁗′	152.0 (s)	–	151.2 (s)	–
1⁗″	90.7 (d)	5.90 (1H, d, 4.5)	89.3 (d)	5.87 (1H, d, 4.5)
2⁗″	75.9 (d)	4.14 (1H, t, 4.5)	72.5 (d)	4.11 (1H, t, 4.5)
3⁗″	71.4 (d)	4.18 (1H, t, 4.5)	69.9 (d)	4.17 (1H, t, 4.5)
4⁗″	86.4 (d)	4.01 (1H, t, 4.5)	84.9 (d)	3.98 (1H, t, 4.5)
5_a⁗″	62.4 (t)	3.83 (1H, dd, 2.6, 9.8)	60.9 (t)	3.80 (1H, dd, 2.8, 9.4)
5_b⁗″		3.73 (1H, dd, 3.3, 9.1)		3.70 (1H, dd, 3.0, 9.2)
		3.45 (4H, s, NH)		3.27 (1H, s. NH)

(1408 cm^{-1}), and ether groups (1271 and 1110 cm^{-1}). The ^1H NMR spectrum of **1** showed the presence of a three overlap signal of methyl groups, resonating at δ_H 2.16 (9H, s) as a singlet, nine overlap signal of nitrogeneted methylene groups, resonating at δ_H 3.49 to 3.60 ppm as doublet signals, five oxygenated methines consist of four resonating at 3.65 (J = 3.6,11.0 Hz, H_2-2′, 2″, 2‴, 2⁗) as quinted signals and one at 4.14 (J = 4.5 Hz, H_2-2) as a triplet signal. Additional functionalities included the signal of two *ortho*-protons pattern resonated at δ_H 5.69 (1H, d, J = 8.4 Hz) and 8.01 (1H, d, J = 8.4 Hz) was also obserbved in ^1H NMR spectrum. The presence of four oxygenated methines at δ_H 4.01 to 5.90 and oxygenated methylene at δ_H 3.83 (J = 2.6, 9.8 Hz) and 3.73 (J = 3.3, 9.1 Hz), were assigned to ribose unit which formed by autohydrolysis reaction of the *O*-gycosyl saccharinic acid (Aspinal, 1976), suggesting the presence of saccharide component in **1**.

A total twenty seven carbon resonances were observed in the ^{13}C NMR spectrum. These were assigned by DEPT and HMQC experiments to two olefinic carbons at δ_C 102.7 and 142.8, one quartenary carbon, two amide carbonyl at δ_C 166.3 and 152.0, originating from lactam ring. The presences of four sp^3 oxygenated methines carbon, nine sp^3 nitrogenated methylenes were assigned to the presence of straight chain with amino hidroxyocthylamino formed by asparagine reaction in **1**, which continued by hydrolysis reaction into aliphatic asparagine chain. In addition, four sp^3 oxygenated methines together with one sp^3 oxygenated methylene also observed in ^{13}C NMR, suggested the presence of a ribose ring in **1**. These functionalities accounted for three out of the total five degrees of unsaturation. The remaining two degrees of unsaturation were consistent to bisamide aliphatic asparagine chain derivative with a ribose and lactam ring.

A comparison of the NMR data of **1** with uridine (Jian et al., 2010), revealed that the structures of the two compounds are closely related in both lactam and ribose ring and different in aliphatic asparagine chain. Position of two amide carbonyl group at C-1⁗ and C-4⁗⁗ together with ribose unit were confirmed on basis of HMBC and ^1H-^1H-COSY spectra (Fig. 2). The down field chemical shift of C-1⁗⁗ at δ_H 90.7 was assigned for oxygenated methine which bonded with a nitrogen atom. The proton of H-1⁗⁗ at (δ_H 5.90, J = 4.5 Hz) was correlated to C-2⁗⁗ (δ_C 102.7), C-3⁗⁗ (δ_C 142.8), and C-4⁗⁗ (δ_C 152.0), suggested the ribose ring was bonded in lactam ring. The down field chemical shift of H-5_a⁗⁗ and H-5_b⁗⁗ at δ_H 3.83 and 3.73, was correlated to C-3⁗⁗ (δ_C 71.4) and C-4⁗⁗ (δ_C 86.4), and C-2⁗⁗ (δ_C 75.9) through a long-range correlation, supported the presence of a ribose ring. The relative stereochemistry of **1**, was established by coupling constant of proton H-1⁗⁗ and H-2⁗⁗ at δ_H 5.90, $^{1,2}J$ = 4.5 Hz and comparison of the typical ^{13}C NMR resonance of C-1⁗⁗ at δ_C 90.7 and other related compounds (Jian et al., 2010), indicated that 1⁗⁗ to be *S* configuration and conformation of axial-equatorial of H-1⁗⁗ and H-2⁗⁗. The down field chemical shift of nitrogenated methylenes at δ_C 64.5 of **1** different to nitrogenated methylenes in aglaithioduline at δ_C 40.1 (Saifah et al., 1999) due to effect of oxygenated methine which bonded in straight chain with amino hidroxyocthylamino together with folding process on amino hidroxyocthylamino chain which cuased by anisotropy effect (Vise et al., 2005; Ramkumar & Ramakrishnan, 2008). The gross structure of straight chain with amino hidroxyocthylamino was deduced from the ^1H-^1H-COSY and HMBC spectra (Fig 2). The oxygenated methine signals, resonated at δ_H 3.65 (4H, *q*, J = 5.2, 11.0 Hz, H-2′, H-2″, H-2‴, H-2⁗) was correlated with nitrogenated methylene carbon signals at δ_C 64.5 corresponding to C-2, C-1′, C-3′, C-1″,C-3″, 1‴, 3‴, 1⁗, 3⁗, indicated the presence of straight-chain amino hidroxyocthylamino which bonded to hydroxyl group that formed by hydroxylation reaction.

The HMBC spectrum showing correlations of the overlap methyl signal with their neighboring carbons, enabled the assignment of the three singlet methyls. The methyl signals at δ_H 2.16 (H_3-4, H_3-5, H_3-6) were correlated to quarternary carbons at C-3 (δ_C 38.7) and methine carbons at C-1 (δ_C 75.9), whereas the methylene signals at δ_H 3.60 (H-2_b) and 3.49 (H-2_a) was correlated to methine carbon signal at C-1 (δ_C 75.9), indicated the secondary hydroxyl and nitrogenated methylene at C-1 and C-2, respectively. Through analysis of the DEPT, ^1H-^1H-COSY, HMQC and HMBC spectra allowed the complete assignment of all protons and carbons (Table 1). The present of amino hidroxyocthylamino chain was shown in the ^1H-^1H-COSY spectra (Fig. 2). The orientation of hydroxyl groups at H-2′, H-2″, H-2‴, H-2⁗ at δ_H 3.65 (J = 5.2, 11.0 Hz) and H-1 at 4.14 (J = 4.5 Hz) were assigned for β-orientation on the basis of coupling constant values. The presence of a ribose moeity in compound **1** was confirmed by acid hydrolysis of **1** yielded a compound which was identified as ribose by comparison of HPLC retention time with standard compound, therefore the structure of **1** was established as new bisamide derivative and was named eximiamide A.

Compound **2** was obtained as yellow oil. $[\alpha]_{20}^{D}$ −24.6 (*c*, 0.1, MeOH), the molecular formula of **2** was established to be $C_{18}H_{31}N_3O_8$ from HR-TOFMS spectrum which showed a $[M-H]^-$ pseudo molecular ion peak *m*/*z* 416.4528 (calcd. for $C_{18}H_{31}N_3O_8$ *m*/*z* 417.4540) together with NMR data (Table 1), thus requiring five degrees of unsaturation. UV spectrum showed absorption peak at λ_{max} nm (log ε) 268 (5.23) suggesting the presence of an α,β-unsaturation ketone group. The presences of hydroxyl, NH asymmetric, amide carbonyl, NH bending, and ether groups in **2** were evidence by IR absorption at ν_{max} 3409, 2935, 1678, 1411, 1271, 1110 cm^{-1}, respectively. The ^1H and ^{13}C NMR spectrum of **2** resembled that of **1** except for signal of straight-chain with amino hidroxyocthylamino. The presence of nitrogenated methylene at δ_H 3.50 and 3.54 corresponding to H-1_a/H-$3'_a$ and H-1_b/H-$3'_b$, respectively, together with an oxygenated methine at δ_H 4.14 (J = 5.2 Hz) identified that the straight-chain of compound **2** is straight-chain with amino hidroxyethylamino. The Proton of H-2′ and H-3′ at δ_H 3.62 (J = 5.8,10.5 Hz) and H-1 at 4.14 (J = 5.2 Hz) were assigned for β-configuration. Therefore the chemical structure of **2** was established as new bismide derivative was named as an eximiamide B.

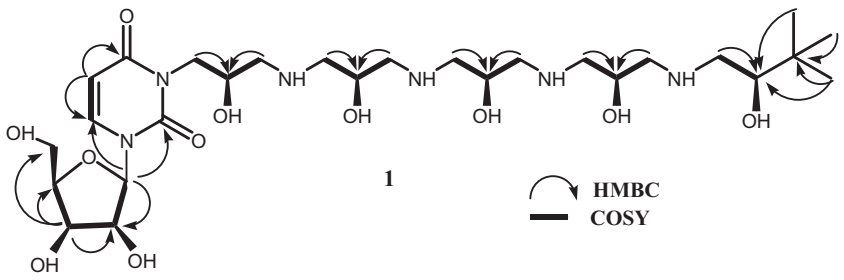

Fig. 2. Selected HMBC correlations for **1**.

The cytotoxicity effects of the two isolated compounds against the P-388 murine leukemia cells were conducted according to the method described in previous paper (Alley et al., 1998) and were used an artonin E (IC_{50} 0.3 μg/mL) as a positive control (Hakim et al., 2007).

Cytotoxic activity of eximiamide A (**1**) and eximiamide B (**2**), was influenced by the presence of hydroxyl, amide carbonyl groups (Harneti et al., 2014; Saifah et al., 1999), and amine functional group, was transformed to be quaternary system by protonation. Insignificant activity of compound **1** than **2**, was influenced by folding process between straight-chain amino hidroxyocthylamino with hydroxyl groups of **1**, it can disturb the amine function transformation to be quaternary system. Unlike compound **1**, folding process of **2** is not occur. These results suggested that a quaternary system moiety from amine function may be an important structural feature for cytotoxic activity in amide structures.

3. Experimental procedure

3.1. General

UV spectra were measured by using Shimazu UV-8452A with methanol. Optical rotations were recorded on an ATAGO AP-300 automatic polarimeter. The IR spectra were recorded on a Perkin-Elmer spectrum-100 FT-IR in KBr. Mass spectra were obtained with a Waters, Qtof HR-MS XEV^{otm} mass spectrometer. NMR spectra were obtained with a JEOL JNM A-500 spectrometer using TMS as internal standard. Chromatographic separations were carried out on silica gel 60 (70–230 and 230–400 mesh, Merck), Octa Desyl Silane (200–400 mesh, Fuji Silysia), PTLC glass plates were precoated with silica gel GF_{254} (Merck, 0.25 mm). Chromatogram of HPLC were obtained with a Waters HPLC 1525 with carbohydrate analysis column, 3.9 × 300 mm. TLC plates were precoated with silica gel GF_{254} (Merck, 0.25 mm) and detection was achieved by spraying with 10% H_2SO_4 in ethanol, followed by heating.

3.2. Plant material

The bark of *A. eximia* were collected in Bogor Botanical Garden, Bogor, West Java Province, Indonesia in June 2011. The plant was identified by the staff of the Bogoriense Herbarium, Bogor, Indonesia and a voucher specimen (No. Bo-1295315) was deposited at the herbarium.

3.3. Extraction and isolation

Dried ground bark (4 kg) of *A. eximia* were extracted successively with *n*-hexane, EtOAc, and MeOH. Evaporation resulted in the crude extracts of *n*-hexane (26.4 g), EtOAc (54.5 g), and MeOH (32.5 g), respectively. The *n*-hexane, ethyl acetate and methanol extracts exhibited a cytotoxic activity against P-388 murine leukemia cells with IC_{50} values of 28, 58 and 40 μg/mL, respectively. The methanol extract (32.5 g) was subjected to vacuum liquid chromatography over silica gel using a gradient elution of mixture of $CHCl_3$/MeOH (10:0–0:10) as eluting solvents to afford 12 fraction (M01–M12). Fraction M05 (1.1 g) was subjected to column chromatography over silica gel using a gradient mixture of EtOAc/MeOH (10:0–4:1) as eluting solvents to afford 12 fraction (N01–N012). Fraction N03 (244.7 mg) was subjected to column chromatography over silica gel using a gradient mixture of $CHCl_3$/MeOH (10:0–4:1) as eluting solvents to afford 25 fraction (O01–O25). Fractions (O10–O15) were combined (70.8 mg) and was preparative TLC on silica gel GF_{254}, eluted with $CHCl_3$: MeOH (4:1), to give **1** (10.4 mg). Fractions (N05–N010) were combined (25.4 mg) and was chromatographed on ODS using a gradient mixture of MeOH–H_2O to afford 5 fractions (P01–P05). Fraction P03 (18.5 mg) was preparative TLC on silica gel GF_{254}, eluted with $CHCl_3$: MeOH (4:1), to give **2** (5.0 mg).

3.3.1. Eximiamide A (*1*)

Yellow oil; $[\alpha]_{20}^{D}$ −10.5 (*c*, 0.1, MeOH); UV MeOH λ_{max} nm (log ε): 262 (5.25); IR (KBr) ν_{maks} cm^{-1}: 3400, 2935, 1681, 1409, 1271, 1110; ^{1}H NMR (CD_3OD, 500 MHz) see Table 1; ^{13}C NMR (CD_3OD, 125 MHz), see Table 1; HR-TOFMS (positive ion mode) *m*/*z* 637.7206 (calcd. for $C_{27}H_{52}N_6O_{11}$ *m*/*z* 636.7354).

3.3.2. Eximiamide B (*2*)

Yellow oil; $[\alpha]_{20}^{D}$ −24.6 (*c*, 0.1, MeOH); UV MeOH λ_{max} nm (log ε) 268 (5.23); IR (KBr) ν_{maks} cm^{-1}: 3409, 2935, 1678, 1411, 1271, 1110; ^{1}H NMR (CD_3OD, 500 MHz) see Table 1; ^{13}C NMR (CD_3OD, 125 MHz), see Table 1; HR-TOFMS (negative ion mode) *m*/*z* 416.4528 (calcd. for $C_{18}H_{31}N_3O_8$ *m*/*z* 417.4540).

3.3.3. Determination of sugar unit in *1*

Compound **1** (2 mg) was hydrolysed with 2 N H_2SO_4 (2 mL) for 1 h at 50 °C. After cooling, the mixture was diluted with 5 mL water and extracted with $CHCl_3$. The aqueous layer was evaporated in reduced pressure to yield a brown residue. The residue was dissolved in MeOH and analyzed by HPLC. The sugar was identified as D-ribose (t_R, 2.88 min) from the hydrolysis experiments with **1** [authentic samples: D-ribose (t_R, 2.88 min)].

3.4. Determination of cytotoxic activity

The cytotoxicity assay was conducted according to the method described by Alley et al. (1998). The P-388 cells were seeded into 96-well plates at an initial cell density of approximately 3.10^4 cells cm^{-3}. After 24 h of incubation for cell attachment and growth, varying concentrations of samples were added. The compounds added were first dissolved in DMSO at the required concentration. Subsequent six desirable concentrations were prepared using PBS (phosphoric buffer solution, pH 7.30–7.65). Control wells received only DMSO. The assay was terminated after a 48 h incubation period by adding MTT reagent [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; also named as thiazol blue] and the incubation was continued for another 4 h, in which the MTT-stop solution containing SDS (sodium dodecyl sulphate) was added and another 24 h incubation was conducted. Optical density was read by using a micro plate reader at 550 nm. IC_{50} values were taken from the plotted graph of percentage live cells compared to control (%), receiving only PBS and DMSO, versus the tested concentration of compounds (μg/mL). The IC_{50} value is the concentration required for 50% growth inhibition. Each assay and analysis was run in triplicate and averaged.

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