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Bisamides from *Aglaia edulis*

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Abstract

The leaves of *Aglaia edulis* afforded a new bisamide, aglaiduline, and two new sulfur-containing bisamides, aglaithioduline and aglaidithioduline. Their structures were established from spectroscopic studies. The sulfur-containing amides exhibited slight antiviral activity against herpes simplex virus types 1 and 2.

Keywords: *Aglaia edulis*; Meliaceae; Bisamides; Aglaiduline; Aglaithioduline; Aglaidithioduline; Anti-herpes simplex virus activity

1. Introduction

Previous phytochemical studies of plants in the genus *Aglaia* (Meliaceae) have revealed the presence of a variety of compounds with interesting biological activities (Duh et al., 1993; Hayashi, Lee, Hall, McPhail & Huang, 1982; Ishibashi, Satasook, Isman & Towers, 1993; Joshi, Chowdhury, Vishnoi, Shoeb & Kapil, 1987; Kiang, Tan, Lim, Habaguchi & Nakanishi, 1982; Ko, Wu, Liou, Huang & Teng, 1992; Saifah et al., 1993). Among these, bisamides, a group of compounds found in several *Aglaia* species, have been reported as exhibiting cytotoxic (Duh et al., 1993; Hayashi et al., 1982) and antiviral activity (Joshi et al., 1987). *Aglaia edulis* A. Gray is a medium-size tree found widely distributed in the central region of Thailand. Recently, a bisamide derived from putrescine, named edulimide, has been found from the leaf extract of this plant (Brader et al., 1998). As a continuation of our investigation of the constituents of the genus *Aglaia* (Saifah, Jongbunprasert & Kelly, 1988; Saifah et al., 1993; Saifah & Suparakchinda, 1998), we have isolated three new bisamides, designated as aglaiduline (**1**), aglaithioduline (**2**) and aglaidithioduline (**3**), from the leaves of *A. edulis*.

2. Results and discussion

The MeOH extract of the leaves was preadsorbed on Kieselguhr and washed down with *n*-hexane, $CHCl_3$ and MeOH, respectively. Chromatographic separation of the $CHCl_3$ eluate yielded compounds **1**–**3**.

The molecular formula of aglaiduline (**1**), $C_{20}H_{24}N_2O_2$, was established from its EIMS molecular ion peak at m/z 324. The presence of only 10 carbon signals in its ^{13}C NMR spectrum suggested a molecule with bilateral symmetry. IR absorptions at 3250 cm^{-1} (N–H) and 1660, 1630, and 1567 cm^{-1} (>N—CO—C=C— stretching region) together with the carbonyl carbon resonance at δ 173.9 revealed the presence of bisamide function in **1**. Comparison of its NMR data with those of pyramidatine (Saifah et al., 1993), another straight-chain bisamide, indicated the

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two methylene proton multiplets at δ 3.15 and 1.47 as representing H_2-2′ (5′) and H_2-3′ (4′), respectively. The phenylacetyl moieties could be determined from a methylene proton singlet at δ 3.46 (H_2-2), three aromatic resonances at δ 7.21 (H-6), 7.26 (H-4 and H-8) and 7.28 (H-5 and H-7) and also by the base peak at *m/z* 91 in the mass spectrum. HMBC experiment displayed the correlation of H_2-2 with the carbon signals at δ 173.9 (C-1), 136.9 (C-3) and 129.9 (C-4 and C-8). A carbon-proton three-bond coupling between H_2-2′ (5′) and C-1 (173.9) was also observed, thus placing phenylacetyl group at both ends of the molecule. Therefore, structure **1** is proposed for aglaiduline.

The ^{1}H NMR spectrum of aglaithioduline (**2**) resembled that of **1** except for three additional signals: a three-proton singlet at δ 2.33 and a pair of doublets (J = 14.7 Hz) at δ 5.79 (H-2″) and 7.53 (H-3″). The Me singlet at δ 2.33, exhibiting a ^{13}C–^{1}H COSY cross peak with a carbon signal at δ 14.3, is typical for S-Me (Greger, Hadacek, Hofer, Wurz & Zechner, 1993). The magnitude of the coupling constant between the latter two vinylic protons indicated a *trans* double bond configuration. In the HMBC spectrum of **2**, the H-3″ proton at δ 7.53 displayed three-bond cross peaks with the carbon signals at δ 167.3 (C-1″) and 14.3 (S-Me), establishing the presence of a (*E*)-3-methylthio-2-propenoyl moiety, which was further supported by the base peak of its mass spectrum at *m/z* 101. According to a long-range correlation observable between C-5′ protons at δ 3.21 and C-1″, this group could be located at one end of the 1,4-butanediamine chain. Hence, compound **2** differs from **1** in that a (*E*)-3-methylthio-2-propenoyl group had replaced one of the two phenylacetyl groups in **1**.

Compound **3**, obtained as pale orange needles from methanol, exhibited a molecular ion peak at *m/z* 288 in its EIMS while displaying only six carbon signals in the ^{13}C NMR spectrum. The resonances ascribable to protons of the phenylacetyl moiety had disappeared, but the existence of two equivalent (*E*)-3-methylthio-2-propenoyl groups, with resonances at δ 5.80 (2H, *d*, J = 14.7 Hz), 7.53 (2H, *d*, J = 14.7 Hz) and 2.33 (6H, *s*), and the 1,4-butanediamine chain, at δ 3.24 (4H, *m*) and 1.55 (4H, *m*), could still be observed. Each (*E*)-3-methylthio-2-propenoyl group could be placed at each end of the 1,4-butanediamine chain, yielding another bisamide structure with bilateral symmetry. Thus, structure **3** is assigned to the compound aglaidithioduline.

All three compounds were subjected to plaque reduction assay (Abou-Karam & Shier, 1990) in order to evaluate their activity against herpes simplex virus (HSV) types 1 and 2. Only the sulfur-containing compounds **2** and **3** displayed slight activity (less than 50% reduction of plaque formation) at the non-cytotoxic concentration of 20 μg/ml.

Previously, sulfur-containing amides had been reported as the constituents of the genus *Glycosmis* of the Rutaceae (Greger, Hadacek, et al., 1993; Greger, Zechner, Hofer, Hadacek & Wurz, 1993; Wu, Chang & Wu, 1995), another family in the same order Rutales as the family Meliaceae. The sulfur-containing groups were considered as deriving from cysteine. Aglaithioduline (**2**) and aglaidithioduline (**3**) represent the first examples of these amides to be isolated from a Meliaceous plant.

3. Experimental

3.1. General

Mps: uncorr.; UV: MeOH; IR: KBr; NMR: 500 MHz (^{1}H) and 125 MHz (^{13}C) in CD_3OD with TMS as int. standard; EIMS: 20 eV; CC: silica gel (Merck 60, 230–400 mesh).

3.2. Plant material

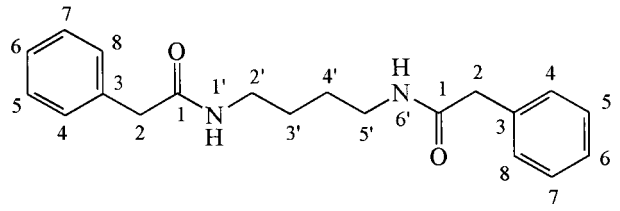
The leaves of *A. edulis* were collected in May 1995 at Pa-la-uu Waterfall in Kangkrajan National Park, Thailand, and were identified by comparison with herbarium specimen (BKF 58415) in the Botany Section, Technical Division, Department of Agriculture, Ministry of Agriculture and Cooperatives, Bangkok, Thailand. A voucher specimen (ES-95051) is deposited with the Herbarium of the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.

3.3. Extraction and isolation

The dried, powdered leaves (2.7 kg) of *A. edulis* were exhaustively extracted with MeOH and filtered. The solvent was then removed in vacuo to give 300 g of the residue, which was mixed with Kieselguhr, packed in a column and eluted with *n*-hexane, $CHCl_3$ and MeOH, successively. The $CHCl_3$ extract (40 g), after removal of the solvent, was suspended in 10% HOAc, filtered, and alkalinized with 25% NH_4OH soln to pH 10. The aqueous phase was partitioned with $CHCl_3$ to yield a fraction (8 g) which was subsequently chromatographed on a column of silica gel eluting with $CHCl_3$–EtOH (26:1) to give compounds **1** (250 mg), **2** (1.20 g) and **3** (191 mg).

3.3.1. Aglaiduline (*1*)

N-[*N*′-(Phenylacetyl)-4-aminobutyl] phenylacetamide. Colourless needles (MeOH), mp 162–163°C; UV



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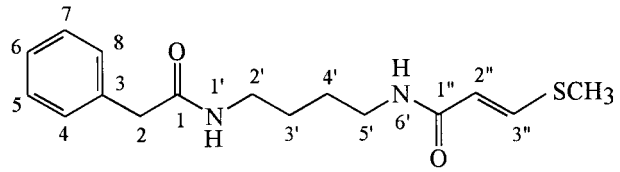

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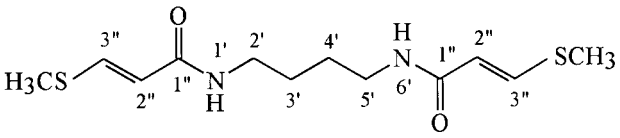

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λ_{max}^{MeOH} nm (log ϵ): 222 (3.53); IR ν_{max}^{KBr} cm^{-1}: 3250, 3067, 1660, 1630, 1567, 767, 683, 617, 550; ^{1}H NMR (500 MHz, CD_3OD): δ 7.28 (4H, *m*, H-5, H-7), 7.26 (4H, *m*, H-4, H-8), 7.21 (2H, *m*, H-6), 3.46 (4H, *s*, H_2-2), 3.15 (4H, *m*, H_2-2′, H_2-5′), 1.47 (4H, *m*, H_2-3′, H_2-4′); ^{13}C NMR (125 MHz, CD_3OD): Table 1; EIMS 20 eV, *m*/*z* (rel. int.): 324 $[M]^+$ (20), 233 (55), 207 (7), 188 (10), 176 (8), 118 (13), 115 (37), 98 (13), 92 (31), 91 (100), 70 (19), 65 (10), 55 (7).

Table 1
^{13}C NMR (125 MHz, CD_3OD) chemical shifts of aglaiduline (**1**), aglaithioduline (**2**) and aglaidithioduline (**3**)

C	1	2	3
1	173.9	174.0	–
2	43.8	43.9	–
3	136.9	137.0	–
4, 8	129.9	130.0	–
5, 7	129.5	129.5	–
6	127.8	127.8	–
2′	40.1	39.9	40.0
3′	27.6	27.7	27.9
4′	27.6	27.8	27.9
5′	40.1	40.1	40.0
1″	–	167.3	167.4
2″	–	116.7	116.8
3″	–	143.4	143.4
-S$\underline{CH_3}$	–	14.3	14.3

3.3.2. Aglaithioduline (*2*)

N-[*N*′-(*E*)-(3-Methylthio-2-propenoyl)-4-aminobutyl] phenylacetamide. Colourless needles (MeOH), mp 140–141°C; UV λ_{max}^{MeOH} nm (log ϵ): 271 (4.40); IR ν_{max}^{KBr} cm^{-1}: 3260, 3125, 2933, 2867, 1680, 1640, 1600, 1550, 1350, 1283, 750, 717; ^{1}H NMR (500 MHz, CD_3OD): δ 7.53 (1H, *d*, *J* = 14.7 Hz, H-3″), 7.29 (2H, *m*, H-5, H-7), 7.27 (2H, *m*, H-4, H-8), 7.22 (1H, *m*, H-6), 5.79 (1H, *d*, *J* = 14.7 Hz, H-2″), 3.47 (2H, *s*, H_2-2), 3.21 (2H, *m*, H_2-5′), 3.18 (2H, *m*, H_2-2′), 2.33 (3H, *s*, S-Me), 1.50 (4H, *m*, H_2-3′, H_2-4′); ^{13}C NMR (125 MHz, CD_3OD): Table 1; EIMS 20 eV, *m*/*z* (rel. int.): 306 $[M]^+$ (7), 291 (4), 259 (3), 215 (10), 189 (13), 188 (12), 124 (12), 101 (100), 91 (54), 73 (14), 70 (31), 65 (9).

3.3.3. Aglaidithioduline (*3*)

N-[*N*′-(*E*)-(3-Methylthio-2-propenoyl)-4-aminobutyl]-(*E*)-3-methylthiopropenamide. Pale orange needles (MeOH), mp 164–165°C; UV λ_{max}^{MeOH} nm (log ϵ): 271 (4.60); IR ν_{max}^{KBr} cm^{-1}: 3310, 3117, 2933, 1640, 1600, 1567, 1350, 1267, 1200, 1016, 967, 850, 643; ^{1}H NMR (500 MHz, CD_3OD): δ 7.53 (2H, *d*, *J* = 14.7 Hz, H-3″), 5.80 (2H, *d*, *J* = 14.7 Hz, H-2″), 3.24 (4H, *m*, H_2-2′, H_2-5′), 2.33 (6H, *s*, S-Me), 1.55 (4H, *m*, H_2-3′, H_2-4′); ^{13}C NMR (125 MHz, CD_3OD): Table 1; EIMS 20 eV, *m*/*z* (rel. int.): 288 $[M]^+$ (2), 273 (3), 241 (6), 171 (18), 156 (7), 124 (20), 101 (100), 73 (20), 70 (19), 58 (9), 45 (8).

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