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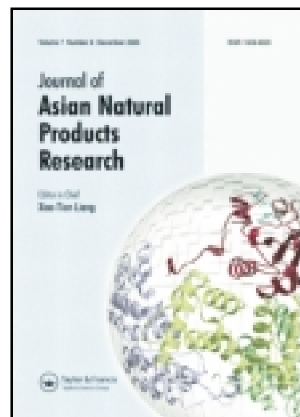

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Chemical constituents from the roots of *Feroniella lucida*

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A new furanocoumarin named lucidafuranocoumarin A (**7**) together with 13 known coumarins (**1–6, 8–14**) and four known alkaloids (**15–18**) was isolated from the roots of *Feroniella lucida*. Their structures were elucidated on the basis of spectroscopic analysis. Some of the isolates were evaluated for their biological activities, and compound **18** showed strong cytotoxicity against KB ($IC_{50} = 0.637\ \mu g/ml$) and NCI-H187 ($IC_{50} = 0.094\ \mu g/ml$) human cancer cell lines, antimalarial activity against *Plasmodium falciparum* ($IC_{50} = 0.336\ \mu g/ml$), and antituberculosis activity against *Mycobacterium tuberculosis* (MIC = 6.25 μg/ml).

Keywords: *Feroniella lucida*; Rutaceae; cytotoxic activity; antimalarial activity; antituberculosis

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1. Introduction

Feroniella lucida (Rutaceae) is locally known as 'Masung' in Thai. It is a medium-sized tree that is distributed widely throughout the northeastern and the north of Thailand. *F. lucida* predominantly produced coumarins, and some of these compounds exhibited antiacetylcholinesterase and cytotoxic activities [1,2]. In our ongoing search for bioactive metabolites from Rutaceae plants [3–5], we report herein the isolation and structure elucidation of a new furanocoumarin (**7**) together with 17 known compounds (**1–6, 8–18**) from the roots of *F. lucida* collected from Nongkhai Province, the northeastern part of Thailand, as well as the biological activities of some isolates (Figure 1).

2. Results and discussion

Compound **7** was isolated as a colorless viscous oil. The molecular formula, $C_{21}H_{22}O_5$, was established by HR-MS, which showed its pseudo-molecular ion peak $[M + H]^+$ at m/z 355.1531 (calcd for $C_{21}H_{23}O_5$ m/z 355.1545). The UV spectrum showed absorption maxima of a conjugated furanocoumarin at 202, 219, 249, 259, 266, and 306 nm [6], whereas the IR spectrum displayed an absorption band of carbonyl functionality at $1732\ cm^{-1}$. The ^1H NMR spectral data (Table 1) of **7** showed the characteristic furanocoumarin framework at δ_H 8.20 (1H, d, $J = 9.6$ Hz, H-4), 7.61 (1H, d, $J = 2.4$ Hz, H-2′), 6.96 (1H, d, $J = 2.4$ Hz, H-3′), and 6.29 (1H, d, $J = 9.6$ Hz, H-3). In addition, the presence of a singlet signal of an aromatic proton was also observed at δ_H 7.17, which identified to be H-8 due to the ^2J and ^3J HMBC correlations (Figure 2) with C-4a (107.3), C-6 (114.0), C-7 (158.0), and C-8a (152.5). Furthermore, the ^1H NMR spectrum also displayed 3-methyl-3-(4-methylpent-3-enyl)oxiran-2-yl)methoxyl group (2″,3″-

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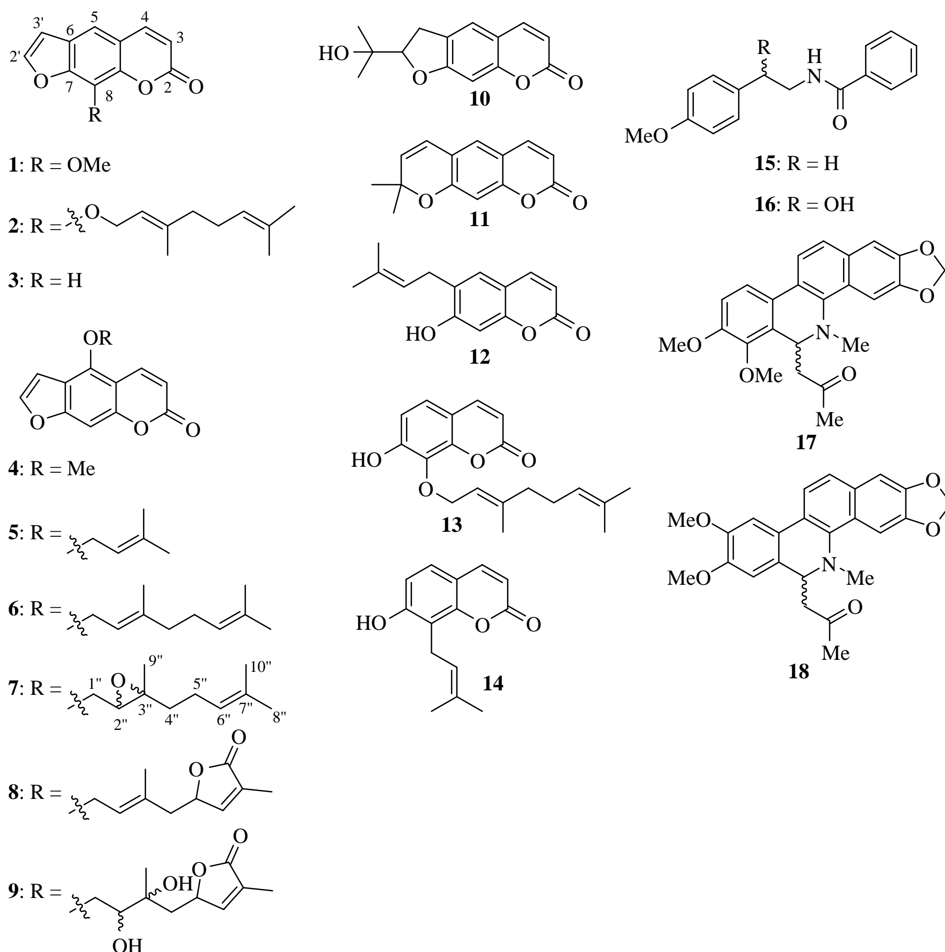

Figure 1. Structures of compounds **1–18.**

epoxygeranyloxy group) at δ_H 5.10 (1H, br t, $J = 7.2$ Hz, H-6″), 4.61 (1H, dd, $J = 10.8$, 4.0 Hz, H-1″a), 4.44 (1H, dd, $J = 10.8$, 6.8 Hz, H-1″b), 3.24 (1H, dd, $J = 6.8$, 4.0 Hz, H-2″), 2.10 (2H, m, H-5″), 1.75 (1H, m, H-4″a), 1.69 (3H, s, H-10″), 1.62 (3H, s, H-8″), 1.50 (1H, m, H-4″b), and 1.33 (3H, s, H-9″). This finding was supported by ^{1}H–^{1}H COSY and HMBC correlations (Figure 2). The ^3J HMBC correlations from H-1″ and H-4 to C-5 (δ_C 148.3) indicated that the side chain moiety was located at C-5 of furanocoumarin framework. Therefore, the structure of **7** was characterized as lucidafuranocoumarin A.

The remaining 17 known compounds were identified as xanthotoxin (**1**) [7], 8-geranyloxypsoralen (**2**) [8], psoralen (**3**) [7], bergapten (**4**) [7], isoimperatorin (**5**) [7], bergamottin (**6**) [9], anisolactone (**8**) [10], 2″,3″-dihydroxyanisolactone (**9**) [11], marmisin (**10**) [12], xanthyletin (**11**) [13], demethylsuberosin (**12**) [14], 8-geranyloxy-7-hydroxycoumarin (**13**) [15], osthenol (**14**) [16], *N*-(4-methoxyphenyl)-benzamide (**15**) [17], terbamide (**16**) [18], 6-acetonyldihydrochelelerythrine (**17**) [19], and 8-acetonyldihydronitidine (**18**) [20] by 1D and 2D NMR spectral data and comparison with their literature data.

Table 1. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectral data of **7** (in $CDCl_3$).

Position	δ_C	δ_H (mult., J in Hz)
2	161.0	–
3	113.0	6.29 (d, 9.6)
4	139.0	8.20 (d, 9.6)
4a	107.3	–
5	148.3	–
6	114.0	–
7	158.0	–
8	94.7	7.17 (s)
8a	152.5	–
2′	145.2	7.61 (d, 2.4)
3′	104.5	6.96 (d, 2.4)
1″	72.2	4.61 (dd, 10.8, 4.0)
		4.44 (dd, 10.8, 6.8)
2″	60.3	3.24 (dd, 6.8, 4.0)
3″	60.7	–
4″	38.2	1.75 (m); 1.50 (m)
5″	23.6	2.10 (m)
6″	123.0	5.10 (br t, 7.2)
7″	132.4	–
8″	17.6	1.62 (s)
9″	16.9	1.33 (s)
10″	25.6	1.69 (s)

As summarized in Table 2, compounds **4**, **5**, **7**–**9**, **11**, **12**, and **18** were evaluated for their cytotoxicity against two human cancer cell lines, oral human epidermoid carcinoma (KB) and human small cell lung cancer (NCI-H187). Among the cytotoxic tested compounds, compound **18** exhibited strong cytotoxicity against KB and NCI-H187 cancer cell lines with the IC_{50} values of 0.637 and 0.094 μg/ml, respectively, which are more potent than those of standard drug ellipticine (Table 2), whereas the remaining compounds were found to be weakly active or not active. Compound **18** was further evaluated for their antimalarial activity against *Plasmodium falciparum* (K1 strain) and antituberculosis activity against *Mycobacterium tuberculosis* (H37Ra strain). The result showed that compound **18** exhibited strong antimalarial activity with the IC_{50} value of 0.336 μg/ml and also showed moderate antituberculosis activity with the MIC_{50} value of 6.25 μg/ml.

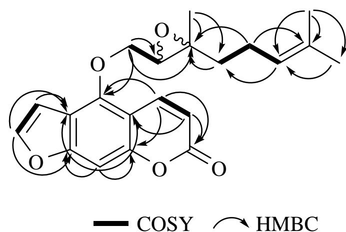

Figure 2. COSY and selective HMBC correlations of **7**.

Table 2. Cytotoxicity of compounds **4**, **5**, **7**–**9**, **11**, **12**, and **18**.

	Cytotoxicity (IC_{50}, μg/ml)	
Compounds	KB	NCI-H187
4	Inactive	Inactive
5	Inactive	Inactive
7	25.58	10.06
8	Inactive	29.30
9	Inactive	Inactive
11	17.97	18.57
12	30.54	17.41
18	0.637	0.094
Ellipticine	1.76	1.06

3. Experimental

3.1 General experimental procedures

The $[\alpha]_D$ value was determined with a Bellingham & Stanley ADP440 polarimeter. The UV spectra were recorded with PerkinElmer UV–Vis spectrophotometer. The IR spectra were recorded with PerkinElmer FTS FT-IR spectrophotometer. The NMR spectra were recorded using 400 MHz Bruker FTNMR Ultra Shield spectrometer. Chemical shifts were recorded in parts per million (δ) in $CDCl_3$ or acetone-d_6 with tetramethylsilane as an internal reference. The ESI-TOF-MS was obtained from microTOF mass spectrometer. Column chromatography was performed by using quick column chromatography (QCC) and column chromatography (CC) were carried out on silica gel 60 H (5–40 μm; Merck, Darmstadt, Germany) and silica gel 100 (63–200 μm; Merck), respectively. Precoated plates of silica gel 60 F_{254} were used for analytical purpose.

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3.2 Plant material

The roots of *F. lucida* were collected from Nongkhai Province, the northeastern part of Thailand, in May 2008. Botanical identification was achieved through comparison with voucher specimen number QBG 30251 in the herbarium collection of Queen Sirikit Botanic Garden, Mae Rim District, Chiang Mai, Thailand, by Asst. Prof. Dr Surat Laphookhieo.

3.3 Extraction and isolation

Air-dried roots of *F. lucida* (7.54 kg) were successively extracted with CH_2Cl_2 over the period of 3 days at room temperature. Removal of the solvent under reduced pressure provided the CH_2Cl_2 extract (200.54 g). This extract was chromatographed by QCC over silica gel eluting with a gradient of *n*-hexane-EtOAc (100% *n*-hexane to 100% EtOAc) to provide 22 fractions (A–V). Upon standing at room temperature, a solid was precipitated from fraction F (550 mg), which was further recrystallized with CH_2Cl_2 to give compound **9** (499.0 mg). Fraction G (15.82 g) was further performed by QCC with a gradient of 100% *n*-hexane to 50% EtOAc-*n*-hexane to give 12 subfractions (G1–G12). Compounds **5** (215.0 mg), **6** (13.2 mg), and **11** (16.5 mg) were obtained from subfraction G4 (799.9 mg) by repeated CC using 10% EtOAc-*n*-hexane as eluent. Fraction G10 (1.05 g) was subjected to CC with 12% EtOAc-*n*-hexane to provide 14 subfractions (G10.1–G10.14). Subfraction G10.5 (100.0 mg) was further purified by CC with 25% CH_2Cl_2-*n*-hexane to give compounds **7** (54.7 mg) and **2** (4.0 mg). Subfractions G10.8 (6.0 mg), G10.12 (30.0 mg), and G10.14 (35.2 mg) were recrystallized with *n*-hexane to yield compounds **3** (2.5 mg), **4** (10.4 mg), and **1** (22.4 mg), respectively. Subfraction G10.11 (32.1 mg) was subjected to CC with 30% CH_2Cl_2-*n*-hexane and yielded compound **17** (7.3 mg). Subfraction G12 (1.60 g) was purified by CC with 70% CH_2Cl_2-*n*-hexane as eluent to give 12 subfractions (G12.1–G12.12). Subfraction G12.2 (34.0 mg) was purified by CC with 18% EtOAc-*n*-hexane to give compound **13** (4.2 mg), whereas compound **14** (4.0 mg) derived from subfraction G12.4 (51.7 mg) by repeated CC using 38% EtOAc-*n*-hexane as eluent. Subfraction G12.7 (20.0 mg) was recrystallized with *n*-hexane to yield compound **15** (12.9 mg). Subfraction G12.12 (266.7 mg) was subjected to CC with 18% EtOAc-*n*-hexane to obtain compound **12** (141.7 mg). Fraction N (3.27 g) was subjected to QCC with 20% EtOAc-*n*-hexane as eluent to afford five subfractions (N1–N5). Compounds **10** (22.6 mg) and **16** (13.6 mg) were obtained from subfraction N2 (160.0 mg) by repeated CC with 2% acetone-*n*-hexane, whereas compound **8** (34.4 mg) was obtained from subfraction N4 (266.9 mg) by repeated CC with 2% EtOAc-CH_2Cl_2. Fraction V (2.06 g) was fractionated by repeated QCC with 5% EtOAc-*n*-hexane to give three subfractions (V1–V3). Subfraction V2 (44.5 mg) was further purified by CC with 40% $CHCl_3$-*n*-hexane to give compound **18** (35.2 mg).

3.3.1 Lucidafuranocoumarin A (7)

A colorless viscous oil; $[\alpha]_D^{25} - 76$ ($c = 0.053$, $CHCl_3$); UV λ_{max} (log ε) (MeOH) nm: 306 (4.16), 266 (4.21), 259 (4.24), 249 (4.33), 219 (4.40), 202 (4.39); IR (neat) ν_{max}: 2967, 2926, 1732, 1625 cm^{-1}. ^1H NMR and ^{13}C NMR spectral data (see Table 1). ESI-TOF-MS: *m/z* 355.1531 $[M + H]^+$ (calcd for $C_{21}H_{23}O_5$, 355.1545).

3.4 Biological assays

3.4.1 Cytotoxic assay

The procedures for cytotoxic assay were performed by the resazurin microplate assay as described by O'Brien *et al.* [21]. Ellipticine was the reference substance in this study, and the IC_{50} values are 1.76 and

1.06 μg/ml for KB and NCI-H187, respectively.

3.4.2 Antimalarial assay

Antimalarial activity was evaluated against the parasite *P. falciparum* (K_1, mutidrug resistant), using the method of Trager and Jensen [22]. Quantitative assessment of *in vitro* malarial activity was determined by means of the microculture radioisotope technique based on the method described by Desjardins *et al.* [23]. The inhibitory concentration (IC_{50}) represented the concentration that caused 50% reduction in parasite growth, which was indicated by the *in vitro* uptake of [^{3}H]-hypoxanthine by *P. falciparum*. The standard compound was dihydroartemisinin ($IC_{50} = 0.0004$ μg/ml).

3.4.3 Antimycobacterial assay

Antimycobacterial activity was evaluated against *M. tuberculosis* (H37Ra strain) employing the green fluorescent protein microplate assay by Changsen *et al.* [24]. The reference drug is isoniazid (MIC = 0.023 μg/ml).

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