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Two new coumarins and a new xanthone from the leaves of *Rhizophora mucronata*

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ABSTRACT

Two new coumarins (**1**, **2**) and a new xanthone (**3**), together with 14 known compounds—eight coumarins (**4**, **5**, **9**, **10**, **12**–**15**), three xanthones (**11**, **16**, **17**), a benzoic acid (**6**) and two flavonones (**7**, **8**)—were isolated from the leaves of *Rhizophora mucronata*. The structures of the compounds were elucidated by spectroscopic (IR, MS, and NMR) analyses. The isolated compounds were tested for cytotoxicity against human cancer cell lines HL-60 and HeLa. Among these compounds, only compound **16** inhibited the growth of both HeLa (IC_{50} = 4.8 μM) and HL-60 (IC_{50} = 1.0 μM) cells. Compounds **4**, **7**, **10**, and **12** exhibited moderate activity against HeLa cells (IC_{50} = 3.8–8.3 μM). Compounds **5**, **9**, **11**, and **17** showed moderate activity against HL-60 cells (IC_{50} = 2.2–6.3 μM). Higher selectivity against HL-60 cell lines was observed for compounds **5**, **9**, **11**, and **16** with SI values (NIH 3T3/HL-60) of 8.6, 19.2, 9.4, and 10.2, respectively.

Mangrove plants, which inhabit the saline swamps near seashores, develop adaptive features such as upright aerial roots and salt-extrusion glands on the leaves.[1] Mangroves consist of approximately 70 species that mainly belong to Rhyizophoraceae, Acanthaceae, Lythraceae, Combretaceae, and Arecaceae families.[2] *Rhizophora mucronata* (Rhyizophoraceae), which is found in the coastal areas of the Indo-Pacific region,[3] is known as red mangrove or Asiatic mangrove.[4] The barks of this species have traditionally been used to treat haematuria, diarrhea, dysentery, and leprosy.[5] Previous studies on this species resulted in the isolation of terpenoids,[6–8] sterols,[6] flavonoids,[9,10] and xanthones,[11] including biologically active compounds such as antioxidant flavonoids[10] and antiinflammatory terpenoids.[12] This work reports the isolation of 17 compounds from the leaves of *R. mucronata* and elucidation of their structures, as well as evaluation of their cytotoxicity against HeLa and HL-60 cell lines.

The MeOH extract of the leaves of *R. mucronata* was subjected to various chromatographic procedures to afford two new coumarins **1**, **2** and a new xanthone **3**, as well as 14 known compounds (see Supplementary data), methoxyinophyllum P (**4**),[13] calocoumarin B (**5**),[14] benzoic acid (**6**), amentoflavone (**7**),[15] naringenin (**8**),[15,16] calophyllolide (**9**),[17] brasimarin C (**10**),[18] 6-deoxy-jacareubin (**11**),[19] inophyllum C (**12**),[20] isocalophyllic acid (**13**),[21] inophyllum E (**14**),[20] calophyllic acid (**15**),[21] jacareubin (**16**),[19,22] and 1,3,5-trihydroxy-2-(3-methylbut-2-enyl)xanthone (**17**)[23] (Fig. 1).

Compound **1** was found to have the molecular formula $C_{26}H_{24}O_5$, as determined by high-resolution electrospray ionization mass spectrometry (HRESIMS) at *m*/*z* 417.1690 $[M+H]^+$ (calcd for 417.1697) together with its NMR data (Table 1).[24] The IR spectrum revealed the presence of an α, β-unsaturated lactone group (1730, 1165 cm^{-1}) and an olefinic C=C bond (1630 cm^{-1}). The ^1H NMR spectrum of **1** showed signals for four methyl, one methoxy, and four olefinic protons, as well as a signal for a monosubstituted benzene ring. In the ^{13}C NMR and HSQC spectra of **1**, 26 carbon signals corresponding to four methyls, one methoxy, nine methines, and ten quaternary carbons, including oxygenated at δ_C, 154.2, 153.6, 152.3, 77.9 and one ketone at δ_C 193.6, as well as the characteristic coumarin carbonyl at 159.6. Detailed HMBC and COSY experiments (Fig. 2) revealed the structure of **1**, which is similar to that of apetatolide (**18**)[25] except for the double bond geometry at C-13 and C-14. The NOESY spectrum observed between H-14 and H-16 suggested the *E*-configuration of the double bond at C-13 and C-14

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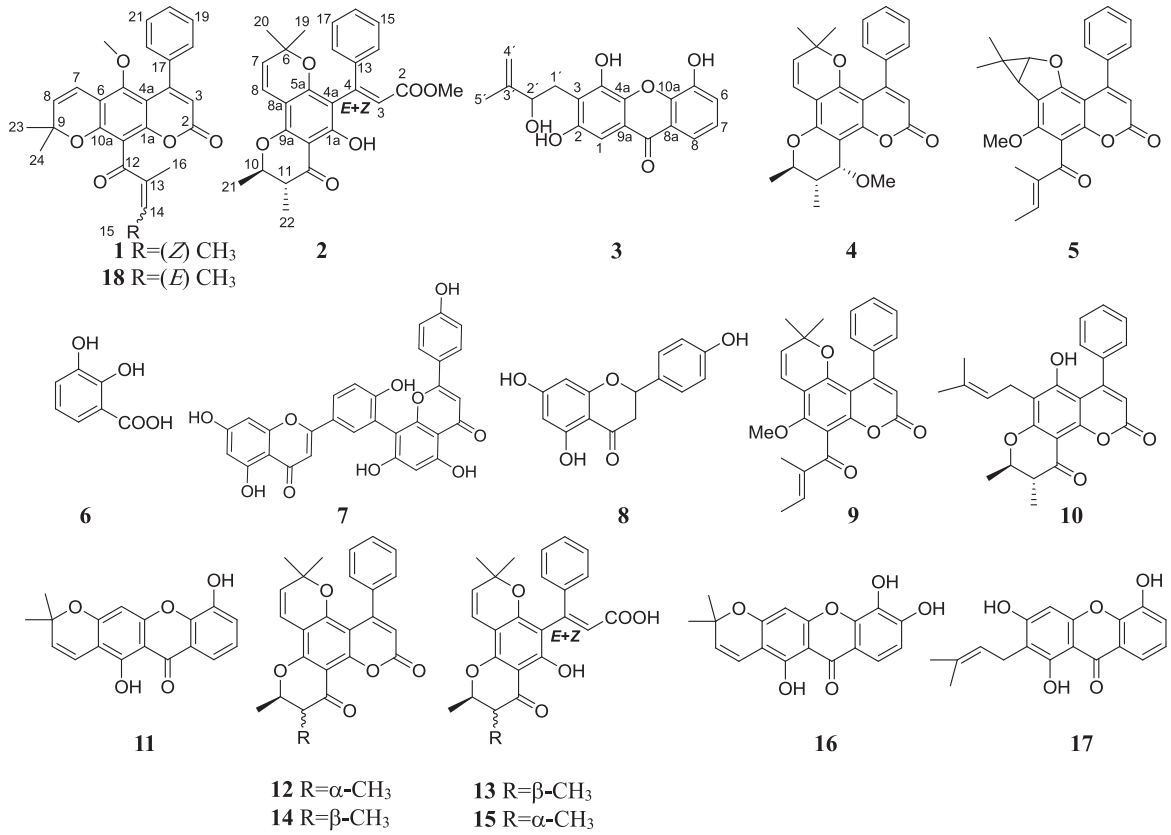

Fig. 1. Structures of compounds **1**–**18**.

Table 1
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data for **1**–**3** in $CDCl_3$.

	1			2			3	
	δ_H mult. (*J* in Hz)	δ_C		δ_H mult. (*J* in Hz)	δ_C		δ_H mult. (*J* in Hz)	δ_C
1a	–	152.3	1a	–	160.4	1	6.53, s	94.8
2	–	159.6	2	–	165.9	2	–	166.1
3	6.04, s	114.3	3	6.47, s	119.1	3	–	109.4
4	–	154.6	4	–	148.2	4	–	162.3
4a	–	106.8	4a	–	108.2	4a	–	103.6
5	–	153.6	5a	–	156.4	5	–	147.4
6	–	112.3	6	–	78.1	6	7.26, dd (7.7, 1.9)	121.3
7	6.47, d (10.1)	115.9	7	5.40, d (10.0)	126.1	7	7.23, t (7.7)	124.8
8	5.66, d (10.1)	130.9	8	6.55, d (10.0)	115.7	8	7.68, dd (7.7, 1.9)	116.4
9	–	77.9	8a	–	101.4	8a	–	122.6
10a	–	154.2	9a	–	158.6	9	–	182.2
11	–	114.2	10	4.25, dq (11.5, 6.2)	78.8	9a	–	157.4
12	–	193.6	11	2.60, dq (11.5, 7.0)	45.7	10a	–	146.6
13	–	139.5	12	–	198.6	1′α	2.93, dd (13.6, 6.5)	29.6
14	6.55, m	143.4	12a	–	101.4	1′β	3.06, dd (13.6, 6.5)	
15	1.89, m	15.1	13	–	140.7	2′	4.45, t (6.5)	76.3
16	1.99, s	10.6	14	7.35, m	128.3	3′	–	148.7
17	–	138.4	15			4′ α	4.63, s	111.1
18	7.39, m	127.5	16			4′ β	4.74, s	
19			17			5′	1.87, s	17.7
20			18					
21			19	0.96, s	27.6			
22			20	1.26, s	28.3			
23	1.38, s	28.0	21	1.53, d (6.2)	19.7			
24	1.38, s	28.0	22	1.21, d (7.0)	10.0			
5-OMe	3.02, s	62.5	2-OMe	3.64, s	51.2			

(angeloyl group at C-11), whereas the configuration for the known compound was *Z* (tigloyl group at C-11) (Table 2).

Compound **2** was obtained as a mixture of *E*, Z-isomers at the C3-C4 double bond (methyl acrylate). The molecular formula was assigned as $C_{26}H_{26}O_6$ by HREIMS (*m*/*z* 434.1720 $[M]^+$ (calcd for 434.1711)).[26] The IR spectrum showed absorption peaks due to phenolic hydroxy (3400 cm^{-1}) and α, β-unsaturated carbonyl groups (1650, 1090 cm^{-1}). The ^{13}C NMR contained 26 carbon sig-