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NEW XANTHONES FROM THE BARKS OF *CRATOXYLUM SUMATRANUM* SSP. *NERIIFOLIUM*

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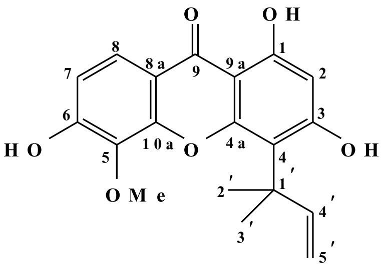
Abstract – Three new prenylated xanthones, neriifolone A-C (**1-3**), and eight known xanthones (**4-11**) were isolated from the barks of *Cratoxylum sumatranum* ssp. *neriifolium*. All the new compounds were characterized by intensive spectroscopic methods (1D and 2D NMR, UV and IR spectroscopy and mass spectrometry).

Cratoxylum is a small genus belonging to the Clusiaceae, which is distributed in several Asian countries. Some species of this genus have been used in folk medicine as a treatment for diarrhea, flatulence[1] as well as diuretic, stomachic and tonic complaints.[2] Xanthone is the major chemical substance present in this genus[3-11] and some of these chemical substances showed interesting biological activities.[4,6-8,10,11] In this paper, we describe the isolation and structural elucidation of three new xanthones (**1**-**3**) together with eight known xanthones (**4-11**) from the barks of *C. sumatranum* ssp. *neriifolium*.

The dichloromethane extract from the barks of *C. sumatranum* spp. *neriifolium* was separated by chromatographic techniques to afford eleven compounds: three new xanthones, neriifolone A (**1**), neriifolone B (**2**) and neriifolone C (**3**), and eight known xanthones (**4-11**). The structures of all of the new compounds were then elucidated using extensive 1D and 2D NMR spectroscopic techniques.



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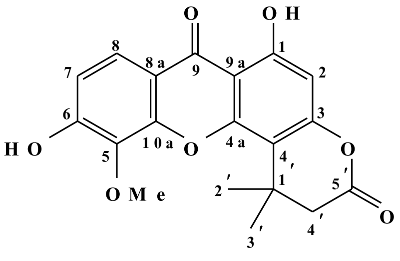

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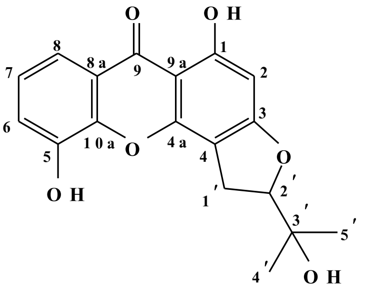

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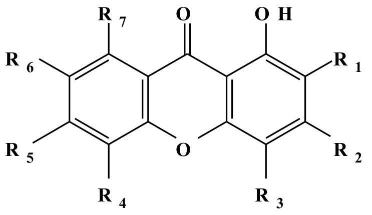
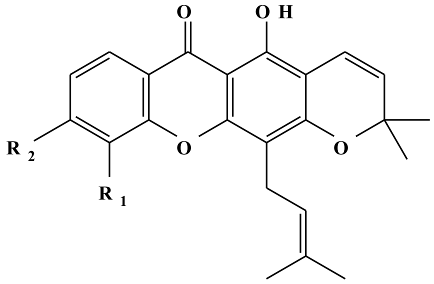
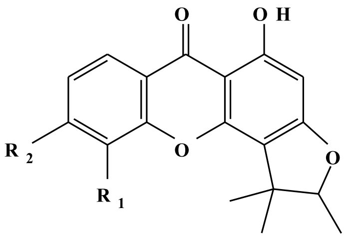


	R1	R2	R3	R4	R5	R6	R7
4	Prenyl	OMe	H	H	OH	OMe	Prenyl
5	H	OH	1,1-dimethylallyl	OH	H	H	H
6	H	OH	1,1-dimethylallyl	OH	OH	H	H



	R1	R2
7	OH	H
8	OMe	OH



	R1	R2
9	OH	H
10	OMe	OH

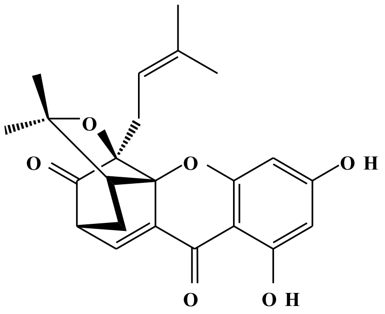


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Figure 1. Compounds isolated from *C. sumatranum* spp. *neriifolium*

Neriifolone A (**1**) was obtained as a yellow solid. The molecular formula, $C_{19}H_{19}O_6$, was determined by HRMS (ESI-TOF) ($[M+H]^+$ *m/z* 343.1194). The UV spectrum showed absorption bands of the xanthone skeleton[8-11] at 246, 256, 320 and 354 nm whereas the IR spectrum showed the stretches for the conjugated carbonyl and hydroxyl functionalities at 1647 and 3392 cm^{-1}, respectively. The ^1H NMR spectrum of **1**

(Table 1) exhibited a signal for a hydrogen bonded hydroxyl group (1-OH) at δ 13.44 and three aromatic protons at δ 7.81 (1H, *d*, J = 8.7 Hz), 7.03 (1H, *d*, J = 8.7 Hz) and 6.32 (1H, *s*) which were assigned to H-8, H-7 and H-2, respectively. Moreover, a methoxy group at δ 3.95 (3H, *s*) and a 1,1-dimethylallyl unit at δ 6.45 (1H, *dd*, J = 17.4, 10.5 Hz, H-4′), 4.96 (1H, *dd*, J = 17.4, 0.9 Hz, Ha-5′) 4.89 (1H, *dd*, J = 10.5, 0.9 Hz, Hb-5′) and 1.77 (6H, *s*, Me-2′ and Me-3′) were also observed in the ^{1}H NMR spectrum. The presence of a 1,1-dimethylallyl unit on C-4 was confirmed by the HMBC correlations (Figure 2) between Me-2′ (δ 1.77), Me-3′ (δ 1.77) and H-4′ (δ 6.45) to C-4 (δ 112.8). The assignment of the methoxy group on C-5 was based on the cross peak of the methoxy protons (δ 3.95) and H-7 (δ 7.03) with C-5 (δ 136.0) in the HMBC experiment.

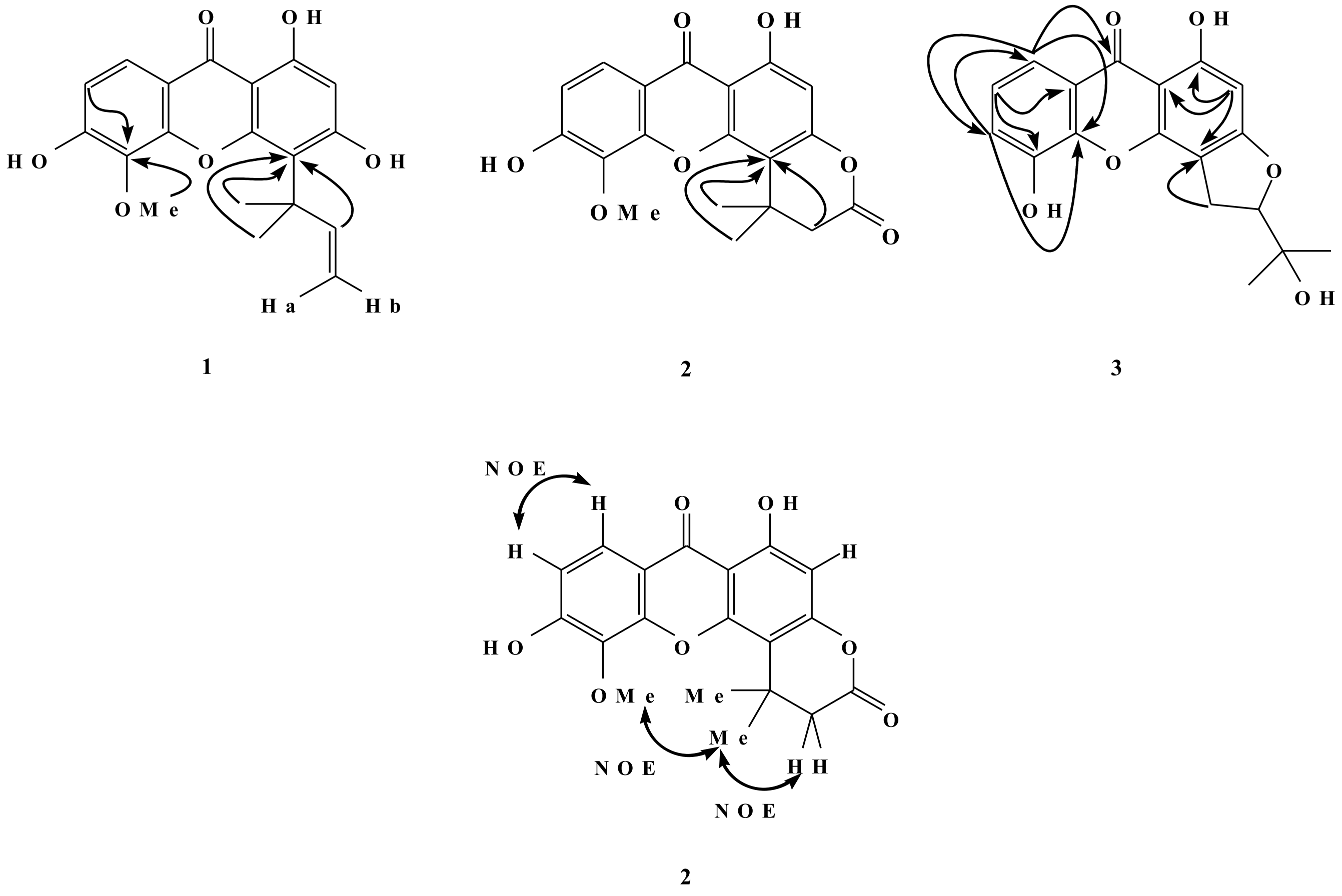

Figure 2. NOE cross peaks of **2** and HMBC correlations of **1**, **2** and **3**

Neriifolone B (**2**) was isolated as a yellow solid. The HRMS (ESI-TOF) gave a molecular ion peak at *m*/*z* 379.0789 ([M+Na]$^{+}$) which was consistent with the molecular formula $C_{19}H_{16}O_{7}$. The UV and IR spectra of **2** exhibited the same pattern as that of **1**. However, the IR spectrum of **2** also showed an additional carbonyl absorption peak at 1780 cm^{-1}. The ^{1}H and ^{13}C NMR spectral data of **2** (Table 1) were similar to those of **1** except for the disappearance of the 1,1-dimethylallyl unit. Compound **2** exhibited signals for the

3,3-dimethyl-δ-lactone ring which showed ^{1}H and ^{13}C NMR signals at δ 1.69/28.0 (Me-2′ and Me-3′), 2.85/45.1 (H/C-4′), 34.8 (C-1′) and 158.1 (C-3), 110.9 (C-4) and 167.0 (C-5′). Based on the HMBC correlations between Me-2′ and Me-3′ (δ 1.69) and H-4′ (δ 2.85) to C-4 (δ 110.9), this unit was placed at C-3 and C-4 of the xanthone skeleton. The cross peak between Me-2′ and Me-3′ (δ 1.69) with 5-OMe (δ 4.01) in the NOE experiment also supported this placement.

Table 1. ^{1}H- and ^{13}C-NMR spectral data of **1**, **2** and **3** in acetone-d_6

Position	**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
1	-	162.6	-	162.8	-	162.1
2	6.32 (*s*)	100.1	6.41 (*s*)	100.2	6.19 (*s*)	100.0
3	-	164.8	-	158.1	-	161.6
4	-	112.8	-	110.9	-	110.6
4a	-	157.0	-	155.5	-	156.7
5	-	136.0	-	135.9	-	147.4
6	-	157.6	-	158.0	7.41 (*dd*, 8.1, 0.6)	120.9
7	7.03 (*d*, 8.7)	114.7	7.09 (*d*, 9.0)	115.4	7.28 (*t*, 8.1)	124.8
8	7.81 (*d*, 8.7)	121.9	7.85 (*d*, 9.0)	122.3	7.68 (*dd*, 8.1, 0.6)	116.1
8a	-	114.7	-	114.7	-	122.3
9	-	181.4	-	181.7	-	182.1
9a	-	103.8	-	106.3	-	105.1
10a	-	151.5	-	151.9	-	146.3
1′	-	42.0	-	34.8	2.03 (*dd*, 13.5, 2.4, *trans*-H) 1.94 (*dd*, 13.5, 7.8, *cis*-H)	46.8
2′	1.77 (*s*)	30.3	1.69 (*s*)	28.0	5.56 (*dd*, 7.8, 2.4)	94.0
3′	1.77 (*s*)	30.3	1.69 (*s*)	28.0	-	109.2
4′	6.45 (*dd*, 17.4, 10.5)	151.2	2.85 (*s*)	45.1	[i]1.75 (*s*)	32.8
5′	4.96 (*dd*, 17.4, 0.9, Ha) 4.89 (*dd*, 10.5, 0.9, Hb)	109.2	-	167.0	[i]1.64 (*s*)	32.8
1-OH	13.44 (*s*)	-	13.28 (*s*)	-	12.98 (*s*)	-
5-OMe	3.95 (*s*)	61.9	4.01 (*s*)	61.9	-	-

[i] Interchangeable

Neriifolone C (**3**) was isolated as a yellow solid. The molecular formula was determined as $C_{18}H_{17}O_6$ by HRMS (ESI-TOF) ($[M+H]^+$ *m*/*z* 329.1018). The UV and IR spectra confirmed that **3** has a xanthone skeleton. Compound **3** exhibited the following ^{1}H NMR (Table 1) signals for the xanthone nucleus. A chelated hydroxyl proton was located at 12.98 ppm. A singlet aromatic proton signal at δ 6.19 which showed ^2J and ^3J HMBC correlations (Figure 2) with C-1 (δ 162.1), C-4 (δ 110.6) and C-9a (δ 105.1) was assigned as the isolated proton H-2. The ABM system of spectrum at δ 7.68 (*dd*, *J* = 8.1, 0.6 Hz), 7.41 (*dd*, *J* = 8.1, 0.6 Hz) and 7.28 (*t*, *J* = 8.1 Hz) and the ^2J or ^3J HMBC correlations of H-6 (δ 7.41) with C-8 (δ 116.1) and C-10a (δ 146.3); H-7 (δ 7.28) with C-5 (δ 147.4) and C-8a (δ 122.3) and H-8 (δ 7.68) with C-6

(δ 120.9), C-9 (δ 182.1) and C-10a (δ 146.3) were assigned as aromatic protons H-8, H-6 and H-7, respectively. Also, a characteristic signal of a 2-(1-hydroxy-1-methylethyl)-2,3-dihydrofuran moiety at δ 1.75 (*s*, H-4′), 1.64 (*s*, H-5′), 5.56 (J = 7.8, 2.4 Hz, H-2′), 2.03 (J = 13.5, 2.4 Hz, *trans*-H) and δ 1.94 (J = 13.5, 7.8 Hz, *cis*-H) and the HMBC correlations of H-1′ (δ 2.03 and 1.94) with C-4 (δ 110.6), confirmed that a 2-(1-hydroxy-1-methylethyl)-2,3-dihydrofuran moiety was fused to the xanthone nucleus at the C-3 and C-4 positions.

The remaining compounds were identified as β-mangostin (**4**),[12] pancixanthone-A (**5**),[13] assiguxanthone-A (**6**),[14] trapezifolixanthone (**7**),[15] 5-*O*-methylxanthone V$_1$ (**8**),[16] pancixanthone-B (**9**),[13] 5-*O*-methyl-2-deprenylrheediaxanthone B (**10**),[17] and (+)-4-oxa-tricyclo[4.3.1.0]decan-2-one scaffold (**11**),[18,19] by 1D and 2D NMR techniques and compared with previous reports of these known compounds.

EXPERIMENTAL

GENERAL

Melting points were measured with using a Bibby Stuart Scientific melting point apparatus SMP3. UV spectra were measured on a UNICAM UV-310 spectrophotometer. Infrared spectra (IR) were recorded on a Perkin-Elmer 1750 FT-IR spectrophotometer. ESI-TOF mass spectra were recorded on a Micromass LCT spectrometer. NMR spectra (^{1}H, ^{13}C, DEPT, ^{1}H-^{1}H COSY, NOESY, HMQC and HMBC) were recorded on Bruker AV300 or AV500 spectrometers. Chromatography was performed with the use of Merck prep-PLC and TLC, Merck silica gel 100 column and Sephadex LH-20 column. Optical rotation was measured in acetone solution with a sodium D line (589 nm) on an AUTOPOL® P-1020 (A068860638) automatic polarimeter.

PLANT MATERIAL

Barks of *C. sumatranum* ssp. *neriifolium* (Clusiaceae) were collected at Amphur Bannasan, Suratthani Province, Thailand, in February 2009. The plant was identified by Assistant Professor Dr. Maruay Mekanawakul, a specialist in the botanics, and the voucher specimen (WU 1453) is deposited at the botanic garden, Walailak University, Nakhon Si Thammarat, Thailand.

EXTRACTION AND ISOLATION

Chopped dried barks of *C. sumatranum* ssp. *neriifolium* (18.5 kg) were extracted with CH_2Cl_2 at room temperature for 3 days. After a removal of solvents, a yellow-brown viscous CH_2Cl_2 extract (366.28 g) was obtained. This extract (366.28 g) was dissolved in acetone. The acetone-soluble portion (255.28 g) was fractionated by quick column chromatography over silica gel 60H with the use of hexane, hexane- CH_2Cl_2, CH_2Cl_2, CH_2Cl_2-acetone, acetone and acetone-MeOH as eluents to afford 10 fractions (FCN1-FCN10).

Fraction FCN5 (8.01 g) was subjected to Sephadex LH-20 column chromatography with MeOH as an eluent, yielding 5 subfractions (FCN5a- FCN5e). **7** (6.4 mg) was obtained from repeated Sephadex LH-20 column chromatography with MeOH as an eluent and then by prep-TLC (CH_2Cl_2: hexane, 3:2 v/v) of subfraction FCN5e (218.7 mg). Repeated Sephadex LH20 gel filtration of fraction FCN6 (20.14 g) gave **4** (32.9 mg), **8** (1.4 mg) and **9** (110.6 mg). Fraction FCN7 (15.52 g) was separated by Sephadex LH-20 column chromatography with MeOH as an eluent, yielding **10** (40.0 mg). Fraction FCN8 (9.16 g) was purified by Sephadex LH-20 column chromatography with MeOH as an eluent and then by prep-TLC (CH_2Cl_2), affording **2** (17.5 mg). Fraction FCN8e (464.5 mg) was separated by Sephadex LH-20 column chromatography with MeOH as an eluent, yielding 6 subfractions (FCN8e1- FCN8e6). Subfraction FCN8e3 (40.4 mg) was purified by prep-PLC (100% CH_2Cl_2) to afford **1** (19.3 mg) while **5** (32.7 mg) and **3** (6.6 mg) were derived from subfraction FCN8e4 (160.0 mg) by prep-PLC (100% CH_2Cl_2). Subfraction FCN8e5 (27.0 mg) and subfraction FCN8-f (50.0 mg) were purified by prep-PLC (100% CH_2Cl_2) to afford **11** (15.0 mg) and **6** (18.9 mg), respectively.

Neriifolone A **1**: Yellow solid. mp 146–147 °C. UV λ_{max} (MeOH) (log ε): 246 (4.08), 256 (3.92), 320 (3.86), 354 (3.38) nm. IR (neat) ν_{max}: 3392 (OH), 1647 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, acetone-d_6) and ^{13}C-NMR (75 MHz, acetone-d_6) see Table 1. TOF-MS $[M+H]^+$ *m/z*: 343.1194 for $C_{19}H_{19}O_6$ (calcd. 343.1176).

Neriifolone B **2**: Yellow solid. mp 231–232 °C. UV λ_{max} (MeOH) (log ε): 244 (4.42), 314 (4.00), 348 (3.77) nm. IR (neat) ν_{max}: 3368 (OH), 1780 (C=O), 1651 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, acetone-d_6) and ^{13}C-NMR (75 MHz, acetone-d_6) see Table 1. TOF-MS $[M+Na]^+$ *m/z*: 379.0789 for $C_{19}H_{16}O_7Na$ (calcd. 379.0788).

Neriifolone C **3**: Yellow solid. mp 297–298 °C. Optical rotation: $[\alpha]_D^{23.6}$ -27.42° (*c* 0.2600 %w/v in acetone). UV λ_{max} (MeOH) (log ε): 248 (4.28), 256 (4.27), 318 (4.02), 366 (3.07) nm. IR (neat) ν_{max}: 3392 (OH), 1651 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, acetone-d_6) and ^{13}C-NMR (75 MHz, acetone-d_6) see Table 1. TOF-MS $[M+H]^+$ *m/z*: 329.1018 for $C_{18}H_{17}O_6$ (calcd. 329.1020).

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