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Abstract

Four new compounds (1-4) together with six known compounds (5-10) were isolated from the leaf extract of *Garcinia nigrolineata*. Compound 4 is a rare tocotrienol quinone dimer. The structures were elucidated based on NMR and MS data. All isolated compounds were evaluated for their antibacterial activities.

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ABSTRACT

Four new compounds (**1-4**) together with six known compounds (**5-10**) were isolated from the leaf extract of *Garcinia nigrolineata*. Compound **4** is a rare tocotrienol quinone dimer. The structures were elucidated based on NMR and MS data. All isolated compounds were evaluated for their antibacterial activities.

Keywords: *Garcinia nigrolineata*, xanthone, tocotrienol, antibacterial activities

1. Introduction

Garcinia is one of the largest genera of the Clusiaceae family. Over 300 species are distributed throughout the tropical and sub-tropical countries [1], with 29 species found in Thailand [2]. *Garcinia* plants produce a variety of bioactive compounds [3-8], however, xanthonenes and benzophenones were the most common compounds isolated from this genus [5-11]. These types of compounds have displayed a wide range of biological activities such as anti-bacterial, cytotoxic, anti-HIV, α -glucosidase inhibitory, antioxidant, anti-inflammatory, antimalarial, and anti-pyretic activities [12-19]. *G. nigrolineata* is a small to medium sized tree widely distributed throughout Malaysia, Thailand and Myanmar. Previous phytochemical investigations, have resulted in the isolation of xanthonenes along with minor compounds including benzopyran, biphenyl, benzoquinone and isoflavone derivatives, and some of these compounds showed antibacterial activity against MRSA [10, 20, 21]. Herein, we report the isolation and structure elucidation of four new compounds, three xanthonenes (**1-3**) and one tocotrienolquinonedimer (**4**), together with six known compounds (Fig. 1) from the leaf extract of *G. nigrolineata* collected from an authentic plant growing in our campus. The antibacterial activities of all isolated compounds are also reported.

2. Experimental

2.1. General

Melting points were measured on a Buchi melting point B-540 visual thermometer or Fisher-Johns melting point apparatus. The UV spectra were recorded with a PerkinElmer or Varian Cary 5000 UV-vis NIR spectrophotometer. IR spectra were recorded on a PerkinElmer FTS FT-IR spectrometer or a Perkin Elmer Frontier Optica FT-IR spectrophotometer. The NMR spectra were recorded on 400 MHz Bruker FT-NMR Ultra Shield and 600 MHz Bruker AV-600 spectrometers with tetramethylsilane as the internal standard. HRESITOFMS spectra were measured on a Bruker-Hewlett-Packard 1100 Esquire-

LC system mass spectrometer. Quick column chromatography (QCC) and column chromatography (CC) were performed on silica gel C60 (0-20 μ m, SiliCycle® Inc.) and silica gel G60 (60-200 μ m, SiliCycle® Inc.), respectively. Sephadex LH-20, when indicated, was also used for CC. Precoated TLC plates of silica gel 60 F254 were used for analytical purposes.

2.2. Plant material

The leaves of *G. nigrolineata* were collected from the authentic plant growing at Mae Fah Luang University, Chiang Rai Province, Thailand (GPS coordinates: 20°03'18.8"N 99°53'38.4"E), in January 2018. A voucher specimen (MFU-NPR0187) was deposited at the Natural Products Research Laboratory of Mae Fah Luang University.

2.3. Extraction and isolation

The fresh leaves of *G. nigrolineata* (1.3 kg) were extracted with acetone (5 L) at room temperature (3 days $\times$ 2) and concentrated under reduced pressure to give an acetone extract (23.4 g). This extract (23.4 g) was separated by QCC eluting with a gradient solvent system of *n*-hexane-acetone (1:0 to 0:1, v/v) to afford six fractions (Fr.1-Fr.6). Fr.1 (3.6 g) was subjected to Sephadex LH-20 CC eluting with CH₂Cl₂-MeOH (2:8, v/v) to afford **4** (7.3 mg). Purification of Fr.2 (5.7 g) by silica gel CC eluting with CH₂Cl₂-*n*-hexane (3:7, v/v) gave **5** (5.3 mg), **6** (6.5 mg), and **7** (8.9 mg). Fr.3 (3.5 g) was purified by Sephadex LH-20 CC (100 % MeOH) followed by silica gel CC eluting with EtOAc-*n*-hexane (4:6, v/v) to yield **1** (1.5 mg) and **8** (2.6 mg). Fr.4 (1.6 g) was purified by Sephadex LH-20 CC (100 % MeOH) followed by silica gel CC eluting with MeOH-CH₂Cl₂ (3:97, v/v) to give **2** (1.4 mg) and **3** (2.3 mg). Compounds **9** (2.1 mg) and **10** (1.7 mg) were obtained from Fr.6 (2.5 g) by silica gel CC eluting with acetone-*n*-hexane (1:1, v/v).

Nigrolineaxanthone X (**1**): yellow gum, $[\alpha]_D^{24} +24.3$ (c 0.1, MeOH), UV (MeOH) $\lambda_{\max}$ (log ϵ) 270 (2.57), 322 (2.64), 366 (2.21) nm. IR (KBr) $\nu_{\max}$ 3377, 2920, 1652, 1617, 1578,

1451, 1397, 1219, 1126, 1014, 942, 774 cm^{-1} . **HRESITOFMS** m/z 397.1652 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{23}\text{H}_{25}\text{O}_6$, 397.1651). ^1H NMR and ^{13}C NMR data, see Table 1.

Nigrolineaxanthone Y (**2**): yellow powder, mp 255-256 $^{\circ}\text{C}$, UV (MeOH) λ_{max} (log ϵ) 267 (4.11), 320 (3.99), 376 (3.69) nm. IR (KBr) ν_{max} 3210, 2967, 1652, 1565, 1348, 1221, 1159, 1113, 785 cm^{-1} . **HRESITOFMS** m/z 399.1806 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{23}\text{H}_{27}\text{O}_6$, 399.1808). ^1H NMR and ^{13}C NMR data, see Table 1.

Nigrolineaxanthone Z (**3**): yellow powder, mp 220-221 $^{\circ}\text{C}$, UV (MeOH) λ_{max} (log ϵ) 248 (3.82), 326 (3.42), 369 (3.29) nm. IR (KBr) ν_{max} 3351, 2969, 2928, 1642, 1581, 1438, 1367, 1224, 904, 771 cm^{-1} . **HRESITOFMS** m/z 439.1738 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{23}\text{H}_{28}\text{O}_7\text{Na}$, 439.1733). ^1H NMR and ^{13}C NMR data, see Table 1.

Nigrolineaquinone B (**4**): red solid, mp 196-197 $^{\circ}\text{C}$, $[\alpha]_D^{24}$ -3.1 (c 0.1, CHCl_3); UV-vis (MeOH) λ_{max} (log ϵ) 226 (3.48), 324 (3.08), 457 (3.31) nm. IR (KBr) ν_{max} 3439, 2924, 1627, 1569, 1449, 1379, 1259, 1093 cm^{-1} . **HRESITOFMS** m/z 819.5567 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{54}\text{H}_{75}\text{O}_6$, 819.5564). ^1H NMR and ^{13}C NMR data, see Table 2.

2.4. Antibacterial assay

The antibacterial assay was determined as recommended by Clinical and Laboratory Standards Institute [22]. All bacterial strains were obtained from the Microbiological Resources Center, Bangkok, Thailand. Gentamicin and vancomycin were used as positive control drugs (Table 3).

3. Results and discussion

The acetone extract was subjected to repeated column chromatography to yield three undescribed oxygenated xanthenes (**1-3**) and one tocotrienol quinone dimer (**4**) together with six known compounds. The known compounds were identified as 8-deoxygartanin (**5**) [9], toxyloxanthone A (**6**) [23], ananixanthone (**7**) [24], nigrolineaxanthone Q (**8**) [10], 3'-

deoxyquercetin (**9**) [25] and 3',3,4',5,7-pentahydroxyflavone (**10**) [26] (Fig. 1 and 3) by comparison of their physical and spectroscopic data with published values.

Nigrolineaxanthone X (**1**) was obtained as a yellow gum. A molecular formula of $C_{23}H_{24}O_6$, was deduced by the combination of its 1H and ^{13}C NMR and HRESITOFMS data [m/z 397.1652 $[M + H]^+$ (calcd for $C_{23}H_{25}O_6$, 397.1651)]. The UV spectrum showed absorption bands at λ_{max} 270, 322 and 366 nm, which are typical of a xanthone chromophore [10, 20-21]. The IR spectrum showed stretching bands for hydroxy (3377 cm^{-1}) and carbonyl (1652 cm^{-1}) functional groups. The 1H and ^{13}C NMR spectroscopic data (Table 1) displayed resonances for a H-bonded hydroxy proton (δ_H 13.54 (1H, s, OH-1), an ABC spin system of aromatic protons [δ_H 7.71 (1H, d, $J = 7.9\text{ Hz}$, H-8), 7.36 (1H, d, $J = 7.9\text{ Hz}$, H-6), and 7.30 (1H, t, $J = 7.9\text{ Hz}$, H-7)], a prenyl unit [δ_H 5.32 (1H, t, $J = 7.2\text{ Hz}$, H-2')/ δ_C 121.3, 3.34 (2H, m, H-1')/ δ_C 21.0, 1.81 (3H, s, H-4')/ δ_C 16.5, 1.68 (3H, s, H-5')/ δ_C 25.0, and δ_C 130.7 (C-3')], and a pyran unit containing OH-2'' group [δ_H 4.91 (1H, t, $J = 8.5\text{ Hz}$, H-2''), 3.41 (2H, m, H-1''), 1.31 (3H, s, H-4''), and 1.30 (3H, s, H-5'')]. The prenyl unit was placed at C-2 due to the 3J HMBC correlations (Fig. 2) of H₂-1' (δ_H 3.34) and OH-1 (δ_H 13.54) to C-2 (δ_C 105.7) while the pyran unit was attached to C-3/C-4 of the fully substituted aromatic ring from the HMBC correlations between H₂-1'' (δ_H 3.41) to C-3 (δ_C 165.4), C-4 (δ_C 103.2), and C-4a (δ_C 149.8). The absolute configuration at C-2'' of **1** was postulated as *S* on the basis of the positive specific rotation value of **1** ($[\alpha]^{24}_D +24.3$, c 0.1, MeOH) and is consistent with those of cochinensoxanthone ($[\alpha]^{20}_D +11$, c 0.1, CH_2Cl_2) [27] and decursinol ($[\alpha]^{26}_D +10.3$, c 0.1, $CHCl_3$) [28]. Therefore, **1** was proposed as (2''*S*)-nigrolineaxanthone X.

Nigrolineaxanthone Y (**2**), a yellow powder, gave an $[M + H]^+$ ion at m/z 399.1806 in the HRESITOFMS data corresponding to the molecular formula $C_{23}H_{26}O_6$ (calcd for $C_{23}H_{27}O_6$, 399.1808). The 1H and ^{13}C NMR data (Table 1) were similar to those of **1** except

that the C-2'' carbinol of **1** was reduced to a C-2'' methylene group in **2**, which displayed resonances at δ_{H} 1.88 (H-2'')/ δ_{C} 30.7. Additionally, the $\Delta^{2'(3')}$ double bond of **1** was hydrated to generate a 3-hydroxy-3-methylbutyl moiety [δ_{H} 2.57 (2H, m, H-1')/ δ_{C} 17.2, 1.49 (2H, m, H-2')/ δ_{C} 42.7, 1.17 (6H, s, H-4' and H-5')/ δ_{C} 28.9, and δ_{C} 69.0 (C-3')] in **2**. The HMBC correlations shown in Figure 2 were fully consistent with the structure of **2**.

Nigrolineaxanthone Z (**3**) was isolated as a yellow powder. The molecular formula $\text{C}_{23}\text{H}_{28}\text{O}_7$ was established on the basis of HRESITOFMS data [m/z 439.1738 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{23}\text{H}_{28}\text{O}_7\text{Na}$, 439.1733)]. The NMR spectroscopic data (Table 1) of **3** were similar to those of nigrolineaxanthone Y (**2**), except for the pyran unit which was opened to generate a 3-hydroxy-3-methylbutyl moiety [$\delta_{\text{H}}/\delta_{\text{C}}$ 3.06 (2H, t, $J = 7.8$ Hz, H-1'')/16.4, 1.82 (2H, t, $J = 7.8$ Hz, H-2'')/41.5, 1.34 (6H, s, H-4'' and H-5'')/28.3, and δ_{C} 70.4 (C-3'')] in **3**. The correlation of H-1'' (δ_{H} 3.06) to C-3 (δ_{C} 160.5), C-4 (δ_{C} 107.5), and C-4a (δ_{C} 152.1) in the HMBC spectrum (Fig. 2) confirmed the location of the 3-hydroxy-3-methylbutyl unit at C-4.

Figure 3 shows a proposed biosynthetic pathway to the xanthenes **1-3** and **5-8**. The key intermediate compound **5** has been shown to be produced from compound **11** by double prenylations at C-2 and C-4 of compound **11** [29]. Hydration of the two prenyl units of **5** would produce **3**. Selective epoxidation of the 2-prenyl and 4-prenyl units of **5** would produce **12** and **13**, respectively. Cyclization of **12** would give **1** while cyclization followed by dehydration of **13** would produce **6**. Dehydration of **1** would yield **7**, which upon reduction of the pyran ring would give **8**. Further hydration of the prenyl unit of **8** would afford **2**.

Nigrolineaquinone B (**4**), a red solid (mp 196-197 °C), was assigned the molecular formula of $\text{C}_{54}\text{H}_{74}\text{O}_6$ based on its molecular ion at m/z 819.5567 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{54}\text{H}_{75}\text{O}_6$, 819.5564) in the HRESITOFMS data. The UV-vis spectrum displayed maxima absorption bands at λ_{max} 226, 324 and 475 nm while its IR spectrum showed bands for

173 hydroxy (3439 cm⁻¹) and carbonyl (1627 cm⁻¹) functionalities. The **pyrano-*p*-quinone**
 174 **methine skeleton** was identified from the following ¹H and ¹³C NMR data: δ_H/δ_C 7.76 (1H, s,
 175 H-26/26')/127.5, 7.06 (1H, s, OH-6/6'), 6.80 (1H, s, H-7/7')/100.8, 2.53 (2H, m, H-4/4')/15.8,
 176 1.80 (2H, m, H-3/3')/29.3, 1.38 (3H, s, H-25/25')/23.4, and δ_C 179.8 (C-5/5'), 146.9 (C-6/6'),
 177 132.3 (C-8/8'), 110.8 (C-4a/4a'), and 79.3 (C-2/2'). The HMBC correlations confirmed the
 178 core structure and are shown in Fig 2. The NOESY cross peak between H-26 (δ_H 7.76) and
 179 H-7 (δ_H 6.80) indicated the *Z* geometry of $\Delta^{8(26)}$ (or $\Delta^{8'(26')}$) double bond. The (3*E*,7*E*)-4,8,12-
 180 trimethyltrideca-3,7,11-trienyl unit was identified by the combination of data from the ¹H,
 181 ¹³C, HSQC, HMBC, and COSY spectra and the comparison of its NMR data with those of
 182 garciniacowol isolated from *G. cowa* [30]. This unit was placed at C-2 of the main core
 183 structure due to the ²*J* and ³*J* HMBC correlations (Fig. 2) of H₂-9/9' (1.80, 1H, m, H-9a/9a'
 184 and 1.71, 1H, m, H-9b/9b') and H₂-10/10' (δ_H 2.14, 2H, m) to C-2/2' (δ_C 79.3). The singlet
 185 methyl group resonance at δ_H 1.38 was assigned to Me-25/25' which was supported by the
 186 HMBC correlation between Me-25/25' and C-2/2' (δ_C 79.3). The *E* geometry of $\Delta^{11(12)}$ (or
 187 $\Delta^{11'(12')}$) and $\Delta^{15(16)}$ (or $\Delta^{15'(16')}$) double bonds **was** confirmed by the NOESY cross peak
 188 between Me-24 (δ_H 1.59) with H₂-10 (δ_H 2.14) and Me-23 (δ_H 1.64) with H₂-14 (δ_H 2.08),
 189 respectively. The C₅₄H₇₄O₆ molecular formula of **4** along with the observation of only 27
 190 unique ¹³C NMR resonances indicated that compound was a symmetrical dimer [31]. A small
 191 specific rotation of **4** ($[\alpha]_D^{24}$ -3.1 (c 0.1, CHCl₃) indicated that the configuration at C-2/C-2'
 192 should be racemic. A possible biosynthetic pathway for **4** (Fig. 4) starts from geranylgeranyl-
 193 PP and homogentisic acid [32]. Oxidation of **14** could give the para quinone methide **15**
 194 which could dimerize resulting in the C-C bond formation of **17** via the intermediate **16**.
 195 **Further oxidation of 17 would afford 4.**

All isolated compounds were tested for their antibacterial activities (Table 3) against Gram-positive (*Bacillus cereus*, *Micrococcus luteus*, *Staphylococcus aureus*, *Staph. epidermidis*, and *Streptococcus mutans*) and Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, and *Shigella flexneri*) bacteria. Unfortunately, only compound **8** demonstrated moderate antibacterial activities against *M. luteus* with a MIC value of 8 $\mu\text{g/mL}$. All other compounds were found to have weak activities (MIC 32-128 $\mu\text{g/mL}$) or were inactive against both Gram-positive and Gram-negative bacteria.

Conflict of interest

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version.

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