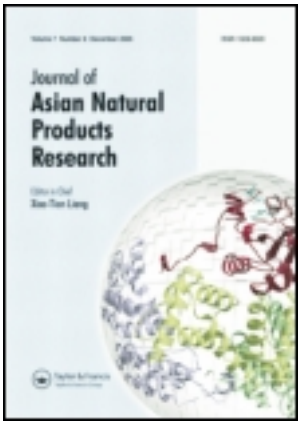

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Two new phenylpropanoids and one propanoate from *Morinda citrifolia*

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Two new phenylpropanoids, methyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate (**1**) and butyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate (**2**), and one unusual propanoate, 5-hydroxyhexyl 2-hydroxypropanoate (**3**), were isolated from the fruits of *Morinda citrifolia*. Their structures were established using MS and NMR methods.

Keywords: *Morinda citrifolia*; Rubiaceae; phenylpropanoids; propanoate

1. Introduction

Morinda citrifolia L. (Rubiaceae), known as 'noni', is a small tree that grows widely across Polynesia [1]. There is a long history of the use of *M. citrifolia* as an important medicinal plant for the treatment of asthma, bone fractures, cancer, cholecystitis, dysentery, lumbago, menstrual cramps, urinary difficulties, and many other ailments [2]. Recent phytochemical studies on this plant have reported anthraquinones and anthraquinone glycosides, fatty acid glycosides, iridoids and iridoid glycosides, lignans, and triterpenoids. Of them, the novel iridoids including citrifolinin A [3], citrifolinoside [4], yopaaoside A [5], yopaaoside B [5], and morindacin [6] were isolated. They showed activities in a wide range of biological assays such as the inhibition of angiogenesis, 5-lipoxygenase and 15-lipoxygenase, cyclooxygenase-1, phorbol ester-induced inflammation and tyrosine kinase [7–11]. Here, we report the isolation of three new compounds, methyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate (**1**), butyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate (**2**), and 5-hydroxyhexyl 2-hydroxypropanoate (**3**) (Figure 1), from the EtOAc and *n*-BuOH extract of the fruits of *M. citrifolia*.

2. Results and discussion

Compound **1** was isolated as a yellow gum. The molecular formula $C_{11}H_{14}O_5$ was established by the positive HR-ESI-MS at *m/z* 249.0745 $[M + Na]^+$. In the ^1H NMR spectrum, two singlets at δ_H 3.81 and 3.68 (each 3H) were assigned to two methoxyl groups, two singlets at δ_H 6.55 and 6.52 (each 1H) were assigned to two aromatic protons, and four protons at δ_H 2.82 and 2.68 (each 2H, t, $J = 6.4$ Hz) were ascribed to protons of two conjoint methylenes. The ^{13}C NMR spectrum displayed 11 carbon resonances ascribable to 2 methoxyl groups

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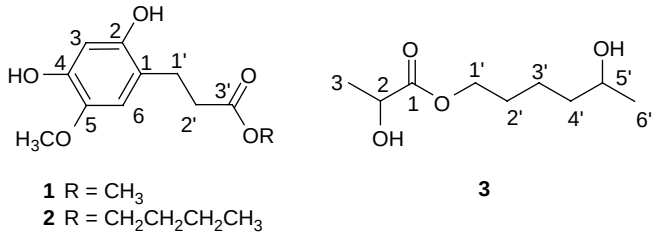

Figure 1. Chemical structures of compounds **1**–**3**.

(δ_C 56.5, 52.3), 2 methylenes (δ_C 23.5, 29.4), 2 methines (δ_C 104.0, 109.6), and 5 quaternary carbons (δ_C 113.0, 138.6, 144.5, 147.4, 169.3). These NMR spectral data suggested that compound **1** was an α,β-saturated phenylpropanoid. One of the methoxyl groups was placed at C-5 according to the HMBC correlation between 5-OCH_3 and C-5, and the ROESY correlation of H-6 with 5-OCH_3 (Figure 2). In addition, the HMBC correlation of the methoxyl at δ_H 3.68 (3H, $-OCH_3$) with C-3′ at δ_C 169.3 suggested a methyl ester group (Figure 2). Detailed analysis of HMBC and ROESY spectra (Figure 2) established the structure of compound **1** as methyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate.

Compound **2** was isolated as a yellow gum. The HR-ESI-MS established the molecular formula $C_{14}H_{20}O_5$ (*m/z* 291.1201 $[M + Na]^+$, calcd 291.1208). All the NMR spectral data suggested that compound **2** had a similar structure to that of **1** except for a *n*-butyl ester in **2** instead of the methyl ester in **1** as suggested by the HMBC correlations of the oxymethylene at δ_H 4.08 (2H, t, $J = 6.5$ Hz) with C-3′ at δ_C 175.4 and the MS data. Detailed analysis of 2D NMR (HSQC, HMBC, $^1H-^1H$ COSY) spectra finally established the structure of compound **2** as butyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate. However, compound **2** might be an artificial product due to the usage of *n*-BuOH in the extraction.

Compound **3** was obtained as a colorless oil. Its molecular formula $C_9H_{18}O_4$ was determined by the negative HR-ESI-MS at *m/z* 189.1127 $[M-H]^-$. The IR spectrum revealed the presence of hydroxyl (3389 cm^{-1}) and carbonyl (1736 cm^{-1}) groups. The ^{13}C NMR spectrum displayed nine carbon resonances including one carbonyl group (δ_C 175.8), two methines (δ_C 66.7, 67.8), four methylenes (δ_C 22.0, 28.5, 38.6, 65.5), and two methyl (δ_C 20.4, 23.6) carbons. Correspondingly, the ^1H NMR spectrum revealed two methyl groups at δ_H 1.19, (d, $J = 6.2$ Hz) and 1.41 (d, $J = 6.2$ Hz), two oxymethines at δ_H 4.27 (m) and 3.79 (m), one oxymethylene at δ_H 4.19 (m), and three methylenes at δ_H 1.44–1.68.

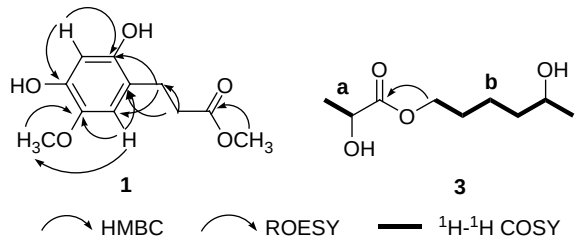

Figure 2. Key 2D NMR correlations of **1** and **3**.

The $^1H-^1H$ COSY spectrum revealed two partial fractions (**a** CH_3CH and **b** $CH_3CHCH_2CH_2CH_2CH_2$) (Figure 2). In the HMBC spectrum, the key correlation of an oxymethylene at δ_H 4.17 (2H, m, H-1′) with C-1 at δ_C 175.8 suggested the connection of partial fractions **a** and **b** via through an ester group (Figure 2). Thus, the planar structure of **3** was determined as 5-hydroxyhexyl 2-hydroxypropanoate. Unfortunately, the stereo configuration at C-2 and C-5′ could not be identified due to the limited quantity available.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured with a Horiba SEPA-300 polarimeter. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. A Tenor 27 spectrophotometer was used for scanning IR spectroscopy using KBr pellets. 1D and 2D NMR spectra were run on Bruker DRX-500 and AM-400 spectrometers with TMS as the internal standard. Chemical shifts (δ) were expressed in ppm with reference to the solvent signals. HR-ESI-MS were performed on an API-Qstar-Pulsar-1 spectrometer. Column chromatography was performed on silica gel (200–300 mesh, Qingdao Haiyang Chemical Co. Ltd., Qingdao, China) and RP-18 gel (20–45 μm, Fuji Silysia Chemical Ltd., Aichi, Japan). Fractions were monitored by TLC (GF 254, Qingdao Haiyang Chemical Co. Ltd.), and spots were visualized by heating silica gel plates sprayed with 10% H_2SO_4 in EtOH.

3.2 Plant material

The dried powder of the fruit of *Morinda citrifolia* was obtained from Hsiehs Biotech., Vietnam in March 2008 and identified by Prof. Hua Peng, and a voucher specimen (YP08019) has been deposited in Hsiehs Biotech., Vietnam.

3.3 Extraction and isolation

Dried noni fruits (1100 g) were extracted with 95% EtOH (1 l) at room temperature for 1 week. The extract was concentrated to dryness under reduced pressure, and the residue was suspended in H_2O (1000 ml) and partitioned successively with EtOAc (3 × 500 ml) and *n*-BuOH (3 × 500 ml). The *n*-BuOH-soluble fraction (61 g) was subjected to column chromatography over silica gel (600 g, 140 cm × 7 cm; $CHCl_3$:Me_2CO = 1:0 → 1:1) to give six subfractions 1–6. Subfraction 5 (4 g) was separated by RP-18 (100 g, 60 cm × 4 cm; MeOH:H_2O = 1:1) to afford **1** (1.1 mg) and **2** (2.5 mg). The EtOAc fraction (21 g) was subjected to column chromatography on silica gel column chromatography (400 g, 60 cm × 4 cm; $CHCl_3$:Me_2CO = 1:0 → 1:1) to afford subfractions 6–9. Subfraction 9 (3 g) was separated by silica gel (100 g, 50 cm × 3 cm; petroleum ether:Me_2CO = 2:1) and further purified by Sephadex LH-20 (30 g, 150 cm × 2 cm; $CHCl_3$:MeOH = 1:1) to yield **3** (2 mg).

3.3.1 Methyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate (1)

Yellow gum; UV (MeOH) λ_{max} (log ε): 204 (3.76), 290 (3.02) nm; IR (KBr) ν_{max}: 3439 (OH), 1737 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 20°C, TMS) and ^{13}C NMR ($CDCl_3$, 20°C, TMS) spectral data, see Table 1. HR MS ((+)ESI): *m/z* 249.0745 $[M + Na]^+$ (calcd for $C_{11}H_{14}O_5Na$, 249.0738).

3.3.2 Butyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate (2)

Yellow gum; UV (MeOH) λ_{max} (log ε): 204 (3.78), 290 (3.16) nm; IR (KBr) ν_{max}: 3441 (OH), 1737 (C=O) $cm^{-1;}$ ^1H NMR ($CDCl_3$, 20°C, TMS) and ^{13}C NMR ($CDCl_3$, 20°C, TMS) spectral data, see Table 1. HR MS ((+)ESI): *m/z* 291.1201 (calcd for $C_{14}H_{20}O_5Na$, 291.1208).

Table 1. ^{1}H and ^{13}C NMR spectral data of **1** and **2** in $CDCl_3$ (δ in ppm, J in Hz).

	1		**2**	
Position	δ_H	δ_C	δ_H	δ_C
1		113.0 (s)		118.0 (s)
2		147.4 (s)		148.6 (s)
3	6.52 (1H, s)	104.0 (d)	6.52 (1H, s)	104.5 (d)
4		138.6 (s)		140.0 (s)
5		144.5 (s)		145.0 (s)
6	6.55 (1H, s)	109.6 (d)	6.55 (1H, s)	112.6 (d)
1′	2.82 (2H, t, 6.4)	23.5 (t)	2.81 (2H, t, 6.4)	24.2 (t)
2′	2.68 (2H, t, 6.4)	29.4 (t)	2.67 (2H, t, 6.4)	35.5 (t)
3′		169.3 (s)		175.4 (s)
5-OCH_3	3.81 (3H, s)	56.5 (q)	3.82 (3H, s)	56.5 (q)
3′-OCH_3	3.68 (3H, s)	52.3 (q)		
$OCH_2CH_2CH_2CH_3$			4.08 (2H, t, 6.5)	65.3 (t)
$OCH_2CH_2CH_2CH_3$			1.58 (2H, m)	30.4 (t)
$OCH_2CH_2CH_2CH_3$			1.33 (2H, m)	19.0 (t)
$OCH_2CH_2CH_2CH_3$			0.90 (3H, t, 7.2)	13.6 (q)

3.3.3 5-Hydroxyhexyl 2-hydroxypropanoate (*3*)

Colorless oil; $[\alpha]_D^{20}$ −20.1 ($c = 0.49$, acetone). IR (KBr) ν_{max}: 3389 (OH), 1736 (C=O), 1459, 1214, 1134 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 20°C, TMS): δ 4.26 (1H, m, H-2), 4.17 (2H, m, H-1′), 3.79 (1H, m, H-5′), 1.68 (2H, m, H-2′), 1.47 (2H, m, H-4′), 1.45 (2H, m, H-3′), 1.40 (3H, d, $J = 6.2$ Hz, H-3), 1.18 (3H, d, $J = 6.2$ Hz, H-6′). ^{13}C NMR (100 MHz, $CDCl_3$, 20°C, TMS): δ 20.4 (q, C-3), 22.0 (t, C-3′), 23.6 (q, C-6′), 28.5 (t, C-2′), 38.6 (t, C-4′), 65.5 (t, C-1′), 66.7 (d, C-2), 67.8 (d, C-5′), 175.8 (s, C-1). HR MS ((−)ESI): m/z 189.1127 $[M-H]^-$ (calcd for $C_9H_{17}O_4$, 189.1126).

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