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A New Organic Acid Derivative from the Fruits of *Rosa roxburghii*

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Abstract: Phytochemical investigation of the fruits of *Rosa roxburghii* resulted in the isolation of four organic acid derivatives and three phenylpropanoids, including a new organic acid derivative, Roxbuacidester A (**1**) and six known compounds (**2-7**). The structures of all isolates were established by 1D and 2D NMR spectra referring to the literatures, together with HR-MS spectrometric analysis. In addition, compounds **1** and **2** were evaluated for their inhibitory activities on nitric oxide (NO) production stimulated by lipopolysaccharide (LPS) in a RAW 264.7 cell line. Compounds **1** and **2** showed moderate inhibition of NO production with IC_{50} values of 46.8 ± 2.3 and 62.5 ± 3.7 μM, respectively.

Keywords: Rosaceae; *Rosa roxburghii*; organic acid derivative.

1. Plant Source

Rosa roxburghii (Rosaceae) is widely distributed in Yunnan, Guizhou and Sichuan provinces of China, and its ripe fruit is primarily used as a food [1]. As a traditional Chinese medicine, the fruit of *R. roxburghii* recorded in "ZhonghuaBencao" was used to treat indigestion, chronic gastritis, stomachache and so on [2]. A series of biological activities, such as antiapoptosis, antitumor, anti-inflammatory, anti-radiation and antimicrobial activity [3-6] have been reported for pure compounds and crude extracts from the fruit of *R. roxburghii*.

The fruit of *R. roxburghii* were collected from Kaili of Guizhou Province (China), and identified by Prof. Sheng-Hua Wei of Guizhou University of Traditional Chinese Medicine. The voucher specimen (No. 20200402) was deposited at Guizhou University of Traditional Chinese Medicine.

2. Previous Studies

In previous phytochemical investigations, the chemical constituents of the fruit of *R. roxburghii* have been reported to be triterpenoids, flavonoids phenylpropanoid, and polysaccharides [3, 7-8].

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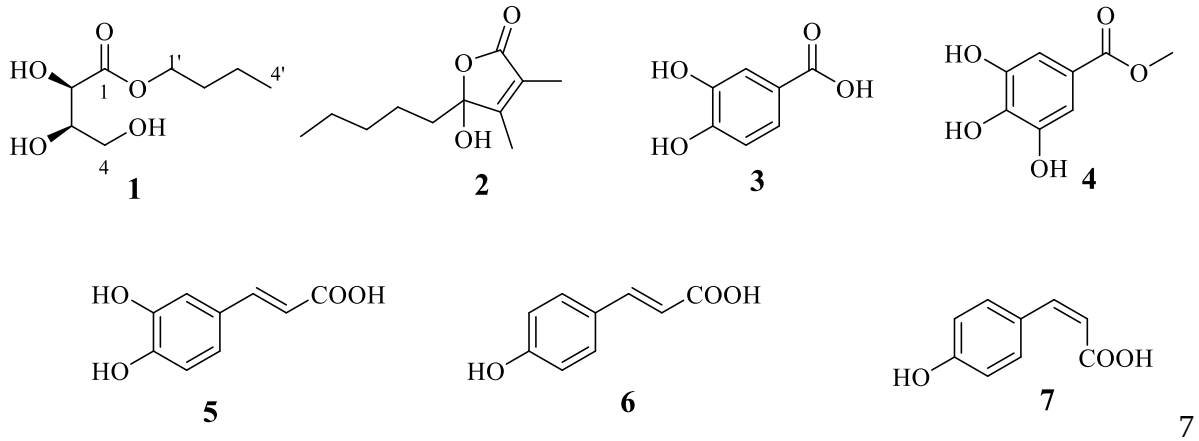

Figure 1. Chemical structures of compounds (**1-7**)

3. Present Study

In this study, the phytochemical composition of the fruit of *R. roxburghii* were carried out, resulting in four organic acid derivatives and three phenylpropanoids, including a new organic acid derivative, Roxbuacidester A (**1**) and six known compounds (**2-7**) (Figure 1). Their structures were determined on the basis of extensive 1D (^{1}H, ^{13}C, DEPT-135) and 2D (HSQC, ^{1}H-^{1}H COSY, HMBC) NMR analyses. And the anti-inflammatory activities of compounds (**1-2)** were evaluated on nitric oxide (NO) production of RAW 264.7 cells model induced by lipopolysaccharide (LPS).

The air-dried the fruit of *R. roxburghii* (8 kg) were extracted with methanol under reflux two times (80 L, 2 h, each). The resulting extracts (243 g) were concentrated under vacuum, suspended in H_2O (5.0 L), and then sequentially partitioned with petroleum ether (PE) (3×5.0 L), ethyl acetate (EtOAc) (3×5.0 L). The ethyl acetate (EtOAc) extracts (78 g) was subjected to silica gel column chromatography eluted with CH_2Cl_2-CH_3OH (1:0-0:1, v/v) to give seven fractions (A-G). Fraction B (3.1 g) was subjected to a sephadex LH-20 column eluted with MeOH (flow rate: 0.8 mL/min) to yield compound **2** (10.2 mg). Fraction C (8.3 g) was separated by ODS column chromatography with MeOH-H_2O (10:90 to 100:0) to afford sub-fractions C1-C8. Sub-fraction C3 (415 mg) was applied to semi-preparative HPLC on C_{18} column (MeOH-H_2O, 47:53; flow rate: 3 mL/min) to yield compounds **1** (3.8 mg, t_R 14.5 min), **3** (18.5 mg, t_R 16.8 min) and **4** (24.4 mg, t_R 22.1 min). Sub-fraction C5 (245 mg) was further purified through semi-preparative HPLC (58:42; flow rate: 3 mL/min) to yield compounds **5** (3.1 mg, t_R 11.5 min), **6** (4.3 mg, t_R 16.6 min) and **7** (8.3 mg, t_R 19.7 min), respectively.

Roxbuacidester A (1): light yellow oil; $[\alpha]_D^{25}$ = +9.0, (c = 0.05, MeOH); HR-ESI-MS: *m/z* 215.0885 $[M+Na]^+$, (calcd. for $C_8H_{16}O_5Na$, *m/z* 215.0889); ^{1}H-NMR (CD_3OD, 400 MHz) and ^{13}C-NMR (CD_3OD, 100 MHz), see Table 1.

Compound **1** was obtained as a light yellow oil with a molecular formula of $C_8H_{16}O_5$ as determined by the HR-ESI-MS (*m/z* 215.0885 $[M+Na]^+$ calcd. for 215.0889). The ^{1}H-NMR data (Table 1) displayed signals for a secondary methyl [δ_H 0.95 (3H, t, *J*=7.4 Hz, H-4′], two oxygenated methylene protons [δ_H 3.65 (1H, dd, *J*=10.8, 7.0 Hz, H-4a], [δ_H 3.57 (1H, dd, *J*=10.8, 6.3 Hz, H-4b], [δ_H 4.18 (2H, t, *J*=6.6 Hz, H-1′] and two oxygenated methane proton [δ_H 4.27 (1H, d, *J*=2.1 Hz, H-2], [δ_H 3.93 (1H, ddd, *J*=7.0, 6.3, 2.1 Hz, H-3]. The ^{13}C NMR data (Table 1) coupled with the DEPT and HSQC spectrum showed carbon resonances corresponding to four methylenes [δ_C 63.5 (C-4), 66.0 (C-1′), 31.8 (C-2′), 20.1 (C-3′)], two methines [δ_C 72.2 (C-2), 74.1 (C-3)], and a carbonyl carbon [δ_C 174.9 (C-4)]. The ^{1}H-^{1}H COSY (Figure 2) correlations of H-2/H-3/H_2-4 and H_2-1′/H_2-2′/H_2-3′/H_3-4′ indicated the presence of two partial structures [-CH-CH-CH_2- and -CH_2-CH_2-CH_2-CH_3]. The HMBC correlations (Figure 2) of H-2/C-1; H_2-4/C-2 and C-3; H_2-1′/C-1 combined with the above NMR signals indicated that compound **1** could be an organic acid ester with a butyl butyrate skeleton and the

N-butanol was attached to the C-1 position. Then, the planar structure of compound **1** was established to be butyl 2,3,4-trihydroxybutanoate. The coupling constant of H-2/H-3 was 2.1 Hz, suggesting the same configurations of 2-OH/3-OH. Thus, **1** was inferred as butyl-2*β*, 3*β*, 4-trihydroxybutanoate, and named Roxbuacidester A.

Table 1. ^{1}H and ^{13}C NMR data of Roxbuacidester A (**1**) (400 and 100 MHz, in CD_3OD)

No	δ_C	δ_H
1	174.9 (C)	-
2	72.2 (CH)	4.27(1H, d, 2.1)
3	74.1 (CH)	3.93(1H, ddd, 7.0, 6.3, 2.1)
4	63.5 (CH_2)	3.65(1H, dd, 10.8, 7.0)
		3.57(1H, dd, 10.8, 6.3)
1′	66.0 (CH_2)	4.18(2H, t, 6.6)
2′	31.8 (CH_2)	1.67(2H, m)
3′	20.1 (CH_2)	1.42(2H, m)
4′	14.0 (CH_3)	0.95(3H, t, 7.4)

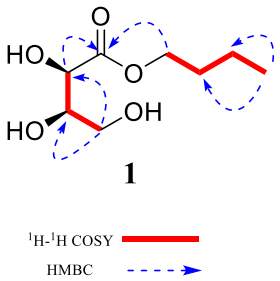

Figure 2. Key HMBC and ^{1}H-^{1}H COSY correlations of compound **1**

The six known compounds were determined by comparison of their NMR data with those reported in the literatures as 5-Hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one (**2**) [9], protocatechuic acid (**3**) [10], methyl gallate (**4**) [11], caffeic acid (**5**) [12], trans-*p*-hydroxy cinnamic acid (**6**)[13], cis-*p*-hydroxy cinnamic acid (**7**) [14] [Figure 1 and Table S1].

An inhibitory assay of NO production was examined in accordance with a method described previously [15-16]. The inhibitory activities against the production of nitric oxide (NO) are summarized in (Table 2). The results suggested that compounds **1** and **2** exhibited moderate inhibition of NO production with IC_{50} values of 46.8 ± 2.3 and 62.5 ± 3.7 μM, respectively.

Table 2. Inhibitory effects of compounds **1-2** on NO production by LPS-induced RAW264.7 cells

Compound	IC_{50} (mean ±SD, μM)
1	46.8 ± 2.3
2	62.5 ± 3.7
Indomethacin*	40.1 ± 3.2

* Positive control

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Supporting Information

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