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CHEMICAL CONSTITUENTS FROM THE LEAVES OF *ALCHORNEA RUGOSA* (LOUR.) MÜLL. ARG. (EUPHORBIACEAE)

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Abstract. *Alchornea* is a genus of plants in the family Euphorbiaceae. It is widely distributed in tropical and subtropical regions of Africa, South Asia, Australia, and Latin America. Many species of the genus *Alchornea* have been used in traditional medicine in some countries around the world. Therefore, there have been many studies focusing on the chemical composition and biological activities of some species of the genus *Alchornea*. In the research project on the chemical composition of 4 species of *Alchornea* distributed in Viet Nam, we have reported compounds isolated from 3 species *A. tiliaefolia*, *A. annamatica*, and *A. trewioides*. *Alchornea rugosa* grows wild throughout Viet Nam and has been used in traditional medicine, but little is known about its chemical composition. From the leaves of species *A. rugosa* collected in Me Linh district, Ha Noi city, Viet Nam, five compounds including 3β-friedelanol (**1**), friedelan-3-one (**2**), methyl syringate (**3**), isovitexin (**4**), and rhoifolin (**5**) has been isolated from the methanol extract from its leaves by different chromatographic techniques. Their chemical structures were determined based on 1D and 2D NMR spectroscopy and mass spectrometry analysis and comparison with reference material. This is the first report on the isolation of these compounds from *A. rugosa*.

Keywords: Alchornea rugosa, 3β-friedelanol, friedelan-3-one, methyl syringate, isovitexin, rhoifolin

Classification numbers: 1.1.1, 1.1.6.

1. INTRODUCTION

The genus *Alchornea* belonging to the Euphorbiaceae family consists of 55 accepted species of deciduous, evergreen trees, or shrubs, which are distributed in many areas in the world. Some *Alchornea* species have been used in traditional medicine to cure edema, measles, acne boils, swelling, and to stop bleeding [1]. Previously, studies on chemical constituents of the *Alchornea* genus showed the presence of phenolic acids, flavonoids, terpenoids, sterols, and alkaloids [2 -5]. In Viet Nam, the plant *A. rugosa* (syn: *A. javanensis*, *A. petalostyla*, *A. hainanensis*, *Adelia glandulosa*, *etc*.; called Bọ nẹt or Sóc dại in Vietnamese) is widely distributed in nature from the North to the South and is used in folk medicine to treat enema and fever, as well as to enhance vitality [6 - 7]. To the best of our knowledge, little is known about the chemical constituents of this plant. Previous studies show that only a few alkaloids have

been isolated from its stem bark [8 - 9]. In this paper, we report the isolation and structural elucidation of five known compounds **1-5** from the leaves of *A. rugosa*.

2. EXPERIMENTS

2.1. General experimental procedures

NMR spectra were recorded on a Bruker AVANCE III HD spectrometer (Bruker, Billerica, MA, USA) using TMS as an internal standard. ESI-MS were measured on an Agilent 1100 LC/MS system. Column chromatography (CC) was carried out on silica gel (230 - 400 mesh, Merck), C18-reversed phase silica gel (100 Å pore size, Fluka), and Sephadex LH-20 gel (25 - 100 µm, Pharmacia Fine Chemical Co. Ltd.). Thin-layer chromatography (TLC) was performed using pre-coated silica gel 60 F_{254} (1.05554.0001, Merck) and RP-18 F_{254S} plates (1.15685.0001, Merck), and compounds were visualized by spraying with 10 % H_2SO_4 solution and heating for 3 - 5 min.

2.2. Plant material

The leaves of *Alchornea rugosa* (Lour) Muell. Arg. were collected in Me Linh, Ha Noi, Viet Nam in April 2016 and identified by Dr. Nguyen Quoc Binh from Vietnam National Museum of Nature, VAST. A voucher specimen (No.VTN/1024) is deposited at the Herbarium of Tay Nguyen Institute for Scientific Research, VAST, Viet Nam.

2.3. Extraction and isolation

The dried leaves of *A. rugosa* (4.4 kg) were extracted with MeOH 96 % (3 × 10 L) at room temperature. The combined methanol extracts were evaporated under reduced pressure to achieve a residue (716 g). The residue was suspended in water (2 L) and then partitioned in turn with *n*-hexane, chloroform, and ethyl acetate to obtain corresponding extracts: *n*-hexane (70 g, H), $CHCl_3$ (77 g, C), EtOAc (189 g, E), and water layer (2 L, W).

The extract H (70 g) was separated by chromatography column (CC) on a silica gel with stepwise gradient elution of *n*-hexane/EtOAc (1:0-0:1, v/v) to yield six fractions, H1-H6. Fraction H1 (24.6 g) was further separated by silica gel CC eluted with *n*-hexane/CH_2Cl_2 (1:1, v/v) to yield seven subfractions, H1.1-H1.7. Subfraction H1.2 (5.3 g) was separated by Sephadex LH-20 CC with MeOH/H_2O (3:1-1:0, v/v) to give four subfractions, H1.2.1-H1.2.4. Subfraction H1.2.4 (272 mg) was separated by silica gel CC eluted with $CHCl_3$/MeOH (5:1) and purified by silica gel CC using *n*-hexane/EtOAc (6:0.5, v/v) to afford compound **1** (25 mg). Fraction H3 (2.1 g) was separated by Sephadex LH-20 column eluted with MeOH/H_2O (1:1 - 1:0, v/v) to give five subfractions, H3.1-H3.5. Subfraction H3.5 (888 mg) was further separated on silica gel CC with CH_2Cl_2/acetone (50:1, v/v) to give four subfractions, H3.5.1-H3.5.4. Subfraction H3.5.1 (26 mg) was subjected to silica gel CC eluted with *n*-hexane/CH_2Cl_2 (1:3, v/v) and purified by RP-C18 column eluted with MeOH/H_2O (9:1, v/v) to yield compound **2** (12 mg).

The extract C (77 g) was separated on silica gel CC with stepwise gradient elution using $CHCl_3$/MeOH (1:0-0:1, v/v) to yield 6 fractions, C1-C6. Fraction C1 (4.8 g) was fractionated by silica gel CC with stepwise gradient elution with CH_2Cl_2/acetone (1:0-0:1, v/v) to yield six subfractions, C1.1-C1.6. Subfraction C1.3 (706 mg) was purified by the RP-C18 column eluted with MeOH/H_2O (3:1, v/v) to give compound **3** (5 mg).

The water layer was passed through Diaion HP-20 CC and eluted first with water and then with MeOH-H_2O (1:3 - 1:0, v/v) to obtain five fractions, W1-W5. Fraction W4 (37 g) was separated on silica gel CC with stepwise gradient elution using $CHCl_3$/MeOH (1:0 - 0:1, v/v) to yield seven subfractions, W4.1-W4.7. Subfraction W4.3 (6.2 g) was subjected to chromatography on Sephadex LH-20 with MeOH/H_2O (1:4-1:0, v/v) to give four subfractions, W4.3.1-W4.3.4. Subfraction W4.3.3 (833 mg) was separated by silica gel CC with $CHCl_3$/MeOH (7:1, v/v) and purified by Sephadex LH-20 CC with MeOH/H_2O (1:4, v/v) to afford compounds **4** (8 mg) and **5** (10 mg).

3β-Friedelanol (1): white crystals, mp. 284.7 ^oC; molecular formula $C_{30}H_{52}O$, ESI-MS *m/z* 429.4 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ_H (ppm): 1.55 (1H, m, H-1a), 1.42 (1H, m, H-1b), 1.90 (1H, dt, *J* = 2.5, 10.0 Hz, H-2a), 1.54 (1H, m, H-2b), 3.73 (1H, brs, H-3), 1.25 (1H, m, H-4), 1.74 (1H, dt, *J* = 3.0, 13.0 Hz, H-6a), 0.99 (1H, m, H-6b), 1.38 (2H, m, H-7), 1.27 (1H, m, H-8), 0.89 (1H, m, H-10), 1.38 (1H, m, H-11a), 1.22 (1H, m, H-11b), 1.32 (2H, m, H-12), 1.47 (1H, m, H-15a), 1.29 (1H, m, H-15b), 1.51 (1H, m, H-16a), 1.34 (1H, m, H-16b), 1.54 (1H, m, H-18), 1.44 (1H, m, H-19a), 1.13 (1H, dt, *J* = 4.5, 13.0 Hz, H-19b), 1.51 (1H, m, H-21a), 1.27 (1H, m, H-21b), 1.46 (1H, m, H-22a), 1.27 (1H, m, H-22b), 0.94 (3H, d, *J* = 7.5 Hz, H-23), 0.97 (3H, s, H-24), 0.86 (3H, s, H-25), 1.01 (3H, s, H-26), 0.99 (3H, s, H-27), 1.00 (3H, s, H-28), 0.95 (3H, s, H-29), 1.17 (3H, s, H-30). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ_C (ppm): 15.81 (C-1), 35.23 (C-2), 72.77 (C-3), 49.21 (C-4), 37.13 (C-5), 41.76 (C-6), 17.57 (C-7), 53.22 (C-8), 38.40 (C-9), 61.39 (C-10), 35.36 (C-11), 30.66 (C-12), 37.86 (C-13), 39.70 (C-14), 32.36 (C-15), 36.11 (C-16), 30.04 (C-17), 42.86 (C-18), 35.58 (C-19), 28.19 (C-20), 32.85 (C-21), 39.30 (C-22), 11.62 (C-23), 16.41 (C-24), 18.26 (C-25), 18.65 (C-26), 20.13 (C-27), 31.81 (C-28), 35.03 (C-29), 32.10 (C-30).

Friedelan-3-one (2): white crystals, mp. 262 - 264 ^oC; molecular formula $C_{30}H_{50}O$, ESI-MS *m/z* 427.2 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ_H (ppm): 1.69 (1H, dd, *J* = 5.0, 13.0 Hz, H-1a), 1.96 (1H, m, H-1b), 2.39 (1H, dd, *J* = 3.5, 13.5 Hz, H-2a), 2.30 (1H, dd, *J* = 6.0, 13.5 Hz, H-2b), 2.25 (1H, q, *J* = 6.5 Hz, H-4), 1.27 (1H, m, H-6a), 1.76 (1H, m, H-6b), 1.39 (1H, m, H-7a), 1.51 (1H, m, H-7b), 1.37 (1H, m, H-8), 1.55 (1H, m, H-10), 1.26 (1H, m, H-11a), 1.45 (1H, m, H-11b), 1.35 (2H, m, H-12), 1.27 (1H, m, H-15a), 1.47 (1H, m, H-15b), 1.58 (1H, m, H-16a), 1.35 (1H, m, H-16b), 1.56 (1H, m, H-18), 1.21 (1H, m, H-19a), 1.38 (1H, m, H-19b), 1.30 (1H, m, H-21a), 1.49 (1H, m, H-21b), 0.93 (1H, m, H-22a), 1.50 (1H, m, H-22b), 0.88 (3H, d, *J* = 6.5 Hz, H-23), 0.73 (3H, s, H-24), 0.87 (3H, s, H-25), 1.00 (3H, s, H-26), 1.01 (3H, s, H-27), 1.18 (3H, s, H-28), 1.05 (3H, s, H-29), 0.95 (3H, s, H-30). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ_C (ppm): 22.3 (C-1), 41.55 (C-2), 213.17 (C-3), 58.26 (C-4), 42.17 (C-5), 41.34 (C-6), 18.27 (C-7), 53.14 (C-8), 37.49 (C-9), 59.53 (C-10), 35.66 (C-11), 30.53 (C-12), 39.73 (C-13), 38.33 (C-14), 32.82 (C-15), 36.05 (C-16), 30.03 (C-17), 42.85 (C-18), 35.38 (C-19), 28.19 (C-20), 32.46 (C-21), 39.28 (C-22), 6.83 (C-23), 14.68 (C-24), 17.96 (C-25), 20.27 (C-26), 18.67 (C-27), 32.12 (C-28), 35.03 (C-29), 31.80 (C-30).

Methyl syringate (3): colourless needles, mp. 103-107 °C, molecular formula $C_{10}H_{12}O_5$, ESI-MS *m/z* 212.9 $[M+H]^+$. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.32 (2H, s, H-2, H-6), 5.88 (1H, brs, 4-OH), 3.94 (6H, s, 3-OMe; 5-OMe), 3.90 (3H, s, 7-OMe). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ_C (ppm): 121.15 (C-1), 106.72 (C-2, C-6), 146,67 (C-3, C-5), 139.25 (C-4), 166.87 (C-7), 56.46 (3-OMe, 5-OMe), 52.09 (7-OMe).

Isovitexin (4): yellow amorphous powder, mp. 220-221 ^oC, molecular formula $C_{21}H_{20}O_{10}$. ESI-MS: *m/z* = 433.0 $[M+H]^+$, 431.0 $[M-H]^-$. ^{1}H-NMR (500 MHz, CD_3OD) δ_H (ppm): 7.86 (2H, d, *J* = 8.5 Hz, H-2′, H-6′), 6.95 (2H, d, *J* = 8.5 Hz , H-3′, H-5′), 6.61 (1H, s, H-3), 6.51 (1H, s, H-

8), 4.93 (1H, d, *J* = 9.5 Hz, H-1″), 4.20 (1H, dd, *J* = 9.0, 9.5 Hz, H-2″), 3.50 (1H, m, H-3″), 3.53 (1H, m, H-4″), 3.45 (1H, m, H-5″), 3.89 (1H, dd, *J* = 2.0, 12.0 Hz, H_a-6″), 3.79 (1H, dd, *J* = 5.5, 12.0 Hz, H_b-6″). ^{13}C-NMR (125 MHz, CD_3OD) δ_C (ppm): 166.11 (C-2), 103.81 (C-3), 183.95 (C-4), 162.84 (C-5), 109.36 (C-6), 166.11 (C-7), 95.55 (C-8), 159.00 (C-9), 105.00 (C-10), 123.17 (C-1′), 129.42 (C-2′), 117.08 (C-3′), 162.84 (C-4′), 117.08 (C-5′), 129.42 (C-6′), 75.45 (C-1″), 72.52 (C-2″), 80.2 (C-3″), 71.64 (C-4″), 82.56 (C-5″), 62.64 (C-6″).

Rhoifolin (5): yellow amorphous powder, mp. 245 ^oC, molecular formula $C_{27}H_{30}O_{14}$, ESI-MS *m/z* 601.0 $[M+Na]^+$. ^{1}H-NMR (500 MHz, CD_3OD) δ_H (ppm): 7.91 (2H, d, *J* = 8.5 Hz, H-2′, H-6′), 6.96 (2H, d, *J* = 8.5 Hz, H-3′, H-5′), 6.81 (1H, d, *J* = 2.0 Hz, H-8), 6.68 (1H, s, H-3), 6.49 (1H, d, *J* = 2.0 Hz, H-6), 5.22 (1H, d, *J* = 8.0 Hz, H-1″), 3.72 (1H, m, H-2″), 3.66 (1H, m, H-3″), 3.63 (1H, m, H-4″), 3.57 (1H, m, H-5″), 3.74/ 3.64 (2H, m, H_a-6″, H_b-6′), 5.30 (1H, d, *J* = 1.5 Hz, H-1‴), 3.45 (1H, m, H-2‴), 3.98 (1H, m, H-3‴), 3.43 (1H, m, H-4‴), 3.96 (1H, m, H-5‴), 1.35 (3H, d, *J* = 6.5 Hz, H-6‴). ^{13}C-NMR (125 MHz, CD_3OD) δ_C (ppm): 166.85 (C-2), 104.15 (C-3), 184.09 (C-4), 162.92 (C-5), 101.03 (C-6), 164.41 (C7), 95.97 (C-8), 159.01 (C-9), 107.0 (C-10), 123.08 (C-1′), 129.66 (C-2′), 117.09 (C-3′), 162.92 (C-4′), 117.09 (C-5′), 129.66 (C-6′), 99.84 (C-1″), 79.16 (C-2″), 78.97 (C-3″), 72.2 (C-4″), 78.27 (C-5″), 62.41 (C-6″), 102.54 (C-1‴), 71.38 (C-2‴), 72.2 (C-3‴), 73.94 (C-4‴), 70.03 (C-5‴), 18.22 (C-6‴).

3. RESULTS AND DISCUSSION

Compound **1** was isolated as white crystals. Its molecular formula, $C_{30}H_{52}O$, was determined by the ESI-MS quasi-molecular ion peak at *m/z* 429.4 $[M+H]^+$. The ^{13}C-NMR and DEPT spectrum indicated that **1** had 30 carbons including eight methyls, eleven methylenes, four sp^3 methines, one oxygenated methine, and six quaternary sp^3 carbons. The ^{1}H-NMR spectra of **1** also showed signals for eight methyl groups at δ_H 0.94 (d, *J* = 7.5 Hz, H-23), 0.97 (s, H-24), 0.86 (s, H-25), 1.01 (s, H-26), 0.99 (s, H-27), 1.00 (s, H-28), 0.95 (s, H-29), and 1.17 (s, H-30). The above data suggested that **1** was a friedelane-type triterpenoid. The presence of a signal at δ_H 3.73 indicated an oxymethine proton. Furthermore, HMBC correlations observed from H-2 (δ_H 1,90/1,54) to C-1 (δ_C 15.81), C-3 (δ_C 72.77), and C-4 (δ_C 49.21), from H-3 (δ_H 3.73) to C-4 and C-23 (δ_C 11.62), from H-23 to C-3, C-4, and C-5 (δ_C 37.13) allowed to confirm an oxymethine proton at C-3 position. Compound **1** was thus identified as 3β-friedelanol and the spectroscopic data compared well with those previously reported [10].

Compound **2** was obtained as white crystals. Its molecular formula, $C_{30}H_{50}O$, was determined by the ESI-MS quasi-molecular ion peak at *m/z* 427.2 $[M+H]^+$. Detailed analysis of the ^{13}C-NMR and HSQC spectra revealed the presence of 30 carbon signals, including eight methyls, eleven methylenes, four sp^3 methines, one carbonyl carbon, and six quaternary sp^3 carbons. Comparison of the ^{1}H- and ^{13}C-NMR data of **2** with those of **1** indicated that the structures of both compounds were similar, except for the replacement of the hydroxymethine group (δ_C 72.77) in **1** with a carbonyl group (δ_C 213.17) in **2**. By comparison of the NMR data of **2** with those of the published data [11], **2** was identified as friedelan-3-one.

Compound **3** was isolated as colorless needle. The ^{1}H-NMR of **3** showed the signals of two protons [δ_H 7.32 (2H, s, H-2 and H-6)] in a tetrasubstituted benzene and three methoxyl groups [δ_H 3.90 (3H, s, 7-OCH_3) and 3.94 (6H, s, 3-OCH_3 and 5-OCH_3)]. The ^{13}C-NMR spectrum combined with the HSQC and HMBC spectral showed signals of 10 carbons, including one carbonyl ester (δ_C 166.87, C-7), three methoxy groups [δ_C 52.09 (7-OCH_3), 56.46 (3-OCH_3 and 5-OCH_3)], and six carbons in the aromatic region [δ_C 121.15 (C-1), 106.72 (C-2, C-6), 146.67

(C-3, C-5), and 139.25 (C-4)]. Accordingly, the structure of **3** was elucidated as methyl syringate by comparison with the spectral data in the literature [12].

Compound **4** was isolated as a yellow amorphous powder. The molecular formula was established as $C_{21}H_{20}O_{10}$ by ESI-MS data ($[M+H]^+$ *m/z* 433.0 and $[M-H]^-$ *m/z* 431.0). The ^{1}H-NMR spectrum of **4** displayed signals of four AA′BB′-type protons [δ_H 7.86 (2H, d, *J* = 8.5 Hz, H-2′, H-6′) and 6.95 (2H, d, *J* = 8.5 Hz, H-3′, H-5′)], one aromatic proton as a singlet at δ_H 6.51 (H-8), one olefinic proton at δ_H 6.61 (H-3). Therefore, the aglycon of **4** was identified as apigenin. The ^{13}C-NMR spectrum of **4** presented signals of 21 carbons, of which 15 carbons were assigned to the flavone aglycone and 6 carbons assigned to the sugar moiety. Its NMR features were also indicative for a *β*-D-glucopyranose [δ_C 75.45 (CH, C-1''), 72.52 (CH, C-2''), 80.2 (CH, C-3''), 71.64 (CH, C-4''), 82.56 (CH, C-5'') and 62.64 (CH_2, C-6'')/δ_H 4.93 (1H, d, *J* = 9.5 Hz, H-1''), 4.20 (1H, dd, *J* = 9.0, 9.5 Hz, H-2''), 3.50 (1H, m, H-3''), 3.53 (1H, m, H-4''), 3.45 (1H, m, H-5''), 3.79 (1H, dd, *J* = 5.5, 12.0 Hz, H_a-6'') and 3.89 (1H, dd, *J* = 2.0, 12.0 Hz, H_b-6 '')]. The HMBC spectrum showed correlations between anomeric proton at δ_H 4.93 (H-1'') of Glc and carbon C-6 at δ_C 109.36 of apigenin, which suggested the glycosylation at C-6 of apigenin skeleton. Based on the NMR spectroscopic data and comparison with literature data [13] the structure of **4** was established as isovitexin.

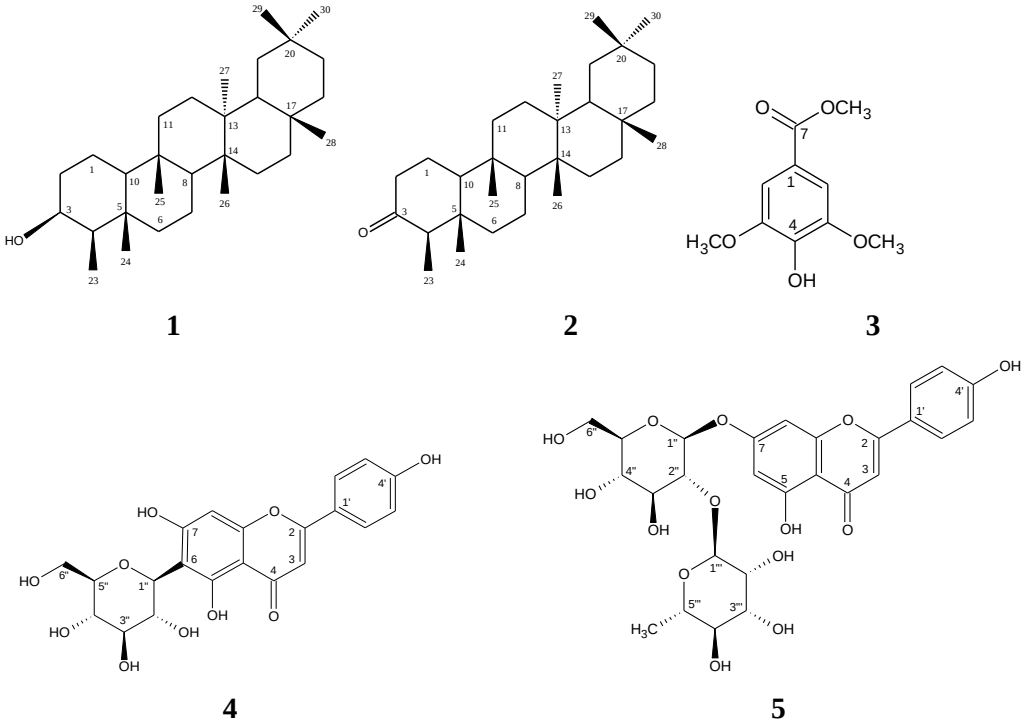

Figure 1. Chemical structures of compounds **1**-**5**.

Compound **5** was isolated as a yellow amorphous powder. The NMR data of **5** revealed the presence of apigenin aglycone and two sugar moieties. The ^{1}H NMR spectra of **5** showed the signals of four AA′BB′-type protons [δ_H 7.91 (2H, d, *J* = 8.5 Hz, H-2′, H-6′) and 6.96 (2H, d, *J* = 8.5 Hz, H-3′, H-5′)], two AX-type aromatic protons [δ_H 6.49 (1H, d, *J* = 2.0 Hz, H-6) and 6.81 (1H, d, *J* = 2.0 Hz, H-8)], and one olefinic proton at δ_H 6.68 (1H, s, H-3). Moreover, the signals

of two anomeric protons at δ_H 5.22 (1H, d, J = 8.0 Hz, H-1'') and 5.30 (1H, d, J = 1.5 Hz, H-1''') were assigned to β-D-glucose (Glc) and α-L-rhamnose (Rha) units, respectively. The ^{13}C-NMR and DEPT spectra of **5** displayed signals of 27 carbons, including 15 carbons of the aglycone and 12 carbons of the sugar moieties. In the HMBC spectrum, H-1''' was shown to correlate with C-2'' (δ_C 79.16), indicating that the α-L-rhamnose was located at the C-2'' position of the glucose moiety. Besides, the HMBC correlation from H-1'' (δ_H 5.22) to C-7 (δ_C 164.41) confirmed the glycosylation at C-7 of aglycon. Based on the spectroscopic evidences and comparison with the reported values in the literature [14], compound **5** was identified as rhoifolin.

4. CONCLUSIONS

From the MeOH extract from the leaves of *Alchornea rugosa*, using various chromatography separations, five compounds 3β-friedelanol (**1**), friedelan-3-one (**2**), methyl syringate (**3**), isovitexin (**4**), and rhoifolin **(5)** were isolated. Their structures were elucidated by 1D and 2D NMR spectroscopic interpretation. This is the first report on the chemical constituents of the species collected in Viet Nam.

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CRediT authorship contribution statement. Author 1: Experimental performance, Methodology, Data analysis, Manuscript preparation. Author 2: Experimental performance, Methodology, Formal analysis. Author 3: Experimental performance, Formal analysis. Author 4: Experimental performance, Methodology, Formal analysis. Author 5: Manuscript revision, Supervision.

Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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