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ORIGINAL ARTICLE

Windienoic acid, a new compound from the medicinal plant *Wikstroemia indica*

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ABSTRACT: A phytochemical investigation of the roots of the medicinal plant *Wikstroemia indica* (Linn.) C. A. Mey led to the isolation of five compounds (**1**–**5**), comprising one previously undescribed metabolite (**1**), named windienoic acid, and four reported compounds (**2**–**5**). The structural elucidation of these compounds was accomplished through comprehensive analysis of spectroscopic data, including 1D (^{1}H and ^{13}C NMR) and 2D NMR techniques (HSQC, COSY, and HMBC). Compounds **2**–**5** were identified as the monoterpene 6,7-dihydroxy-3,7-dimethyl-2-octenoic acid (**2**), the dibenzylbutyrolactone-type lignans (−)-nortrachelogenin (**3**) and (−)-trachelogenin (**4**), and the furofuran-type lignan pinoresinol (**5**) by comparing with literature data. Notably, the structure of compound **1** incorporated an extended conjugated system comprising a dienone moiety linked to a carboxylic acid group, which is rarely in acyclic compound, its structure was confirmed by ^{13}C NMR calculation. The NMR assignment of dihydroxy-3,7-dimethyl-2-octenoic acid (**2**) is reported herein for the first time in methanol-d_4. The cytotoxic screening assay against the A549 human lung cancer cell line of all compounds revealed that compound **3** exhibited weak activity with an IC_{50} value of 42.3 μM.

Keywords: *Wikstroemia indica*, windienoic acid, cytotoxicity

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1 Introduction

Wikstroemia indica (L.) C.A. Mey., a plant of the Thymelaeaceae family, is widely distributed throughout southern China, including provinces such as Zhejiang, Jiangxi, Fujian, Taiwan, Hunan, Guangxi, and Guangdong. The roots and leaves are used medicinally, it has long been used in traditional medicine for its functions of clearing heat and toxins, reducing phlegm, alleviating pain, diminishing swelling, and resolving masses (Editorial Committee of Zhonghua Bencao, 1999). It is commonly prescribed for conditions such as bronchitis, lymphadenitis, rheumatoid arthritis, and traumatic injuries. Based on its anti-inflammatory and detoxifying properties, formulated preparations like Liaogewang Tablets have been developed and are used clinically to treat bronchitis, pneumonia, tonsillitis, mumps, mastitis, and cellulitis. Previous chemical studies of this plant resulted in the isolation of lignans (Chang et al., 2017; Wang et al., 2005; Kato et al., 1979), coumarin and its glycosides (Shi et al., 2022; Wang et al., 2018), guaiane-type sesquiterpene (Liu et al., 2020; Niu et al., 2024), diarylpentanone (Wang et al., 2018; Liu et al., 2021), biflavonoids and flavones (Wang et al., 2018; Shao et al., 2016; Li et al., 2012).

2 Materials and Methods

2.1 Plant Source

The The roots of *Wikstroemia indica* (Linn.) C. A. Mey used in this study were collected in October 2023 from Yulin City, Guangxi Province, China. A sample (202310-Wikin-Td) of the plant material was deposited in Zhejiang Chinese Medical University and identified by the author Danhong Tao with reference to a voucher specimen (PE 02423338) preserved at the Institute of Botany, Chinese Academy of Sciences.

2.2 Extraction and Isolation

Phytochemical studies on the roots of *Wikstroemia indica* led to the isolation of five compounds (Figure 1).

The roots of *Wikstroemia indica* (1.2 kg) were air-dried, powdered, and exhaustively percolated with 95% ethanol (3 × 10 days). The combined extract was concentrated under reduced pressure to afford a crude residue (102 g), which was subjected to sequential liquid–liquid partitioning with ethyl acetate (300 mL × 3) and *n*-butanol (300 mL × 3). The

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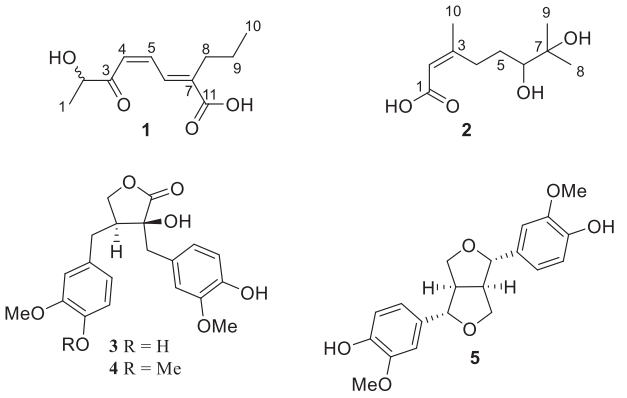

Figure 1. The structures of compounds **1–5** from the roots of *Wikstroemia indica*

ethyl acetate-soluble portion (32 g) was chromatographed over ODS reverse-phase column chromatography eluted with a stepwise gradient of EtOH–H_2O (90:10 → 70:30 → 50:50 → 20:80 → 10:90 → 0:100, v/v) to yield 6 fractions (A1–A6, corresponding to 10%, 30%, 50%, 70%, 90%, and 100% EtOH eluates). Fraction A3 (2.1 g) was further separated by ODS reverse-phase column chromatography using a gradient of MeOH–H_2O (20% to 100% MeOH, v/v), yielding seven subfractions (A4a–A4f). A4c was purified by HPLC using a C-18 column (40% MeOH) to give compounds **1** (1.8 mg, t_R 12.6 min) and **2** (2.5 mg, t_R 17.5 min). Fr.A4 (4.9 g) was rechromatographed on an ODS silica gel column with a MeOH–H_2O gradient (10% to 100% MeOH) to afford five subfractions (A5a–A5e). Fraction A5a was purified by preparative HPLC using a mobile phase of MeOH-H_2O (50:50, 2 mL/min, 210 nm), yielding compound 3 (2.7 mg, t_R = 31 min). Fraction A5b was further separated and purified by HPLC under the same conditions (mobile phase: MeOH-H_2O 50:50, 2 mL/min; 210 nm), affording compounds **4** (3.0 mg, t_R = 27 min) and **5** (3.2 mg, t_R = 33 min).

Windienoic acid (**1**): A light yellow oil; $[\alpha]^{25}_D$ 0 (*c* 0.1, MeOH); ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 211.0972 $[M - H]^-$ (calcd. for $C_{11}H_{15}O_4$, 211.0976).

2.3 Cell Culture and Cell Counting Kit-8 Assay

The A549 cells were maintained in Ham's F-12K medium with 10% FBS and 1% penicillin-streptomycin at 37 °C under 5% CO_2. For the assay, 5 × 10^3 cells per well were plated in 96-well plates and left to adhere overnight. Following a 72-hour exposure to the test compounds, the medium was replaced with 100 µL of fresh medium containing 10% CCK-8 solution. After a 1-hour incubation in the dark, absorbance at 450 nm was recorded on a Thermo Fisher Scientific microplate reader. IC_{50} values were calculated using GraphPad Prism.

3 Results and Discussion

3.1 Structure Elucidation

Compound **1** was obtained as a light yellow oil, its molecular formula $C_{11}H_{16}O_4$ was determined by the negative HRESIMS ion peak at 211.0972 $[M-H]^-$ (calcd. for $C_{11}H_{15}O_4$, 211.0976), requiring the presence of four degrees of unsaturation. The ^{1}H NMR spectrum showed signals for three olefinic protons in a spin system including two protons [δ_H 7.01 (1H, dd, *J* = 12.0, 11.6 Hz) and 6.57 (1H, d, *J* = 11.6 Hz)] for a double bond and a one-proton doublet at δ_H 8.27 (1H, d, *J* = 12.0 Hz) (which was coupled to the proton at δ_H 7.01), a quartet for one oxygenated proton [δ_H 4.29 (1H, q, *J* = 6.9 Hz)], a two-proton multiplet at δ_H 1.48 due to a methylene, a two-proton triplet at δ 2.50 ascribable to a methylene, a methyl doublet [δ_H 1.33 (1H, d, *J* = 6.90 Hz)], and a methyl triplet [δ_H 0.93 (1H, t, *J* = 7.2 Hz)]. The ^{13}C NMR spectrum of **1** (Table 1) showed 9 carbons, which were classified as a carbonyl carbon (δ_C 204.5), three olefinic carbons (δ_C 138.5, 134.1, 126.5), one oxymethine (δ_C 74.5), four methylenes (δ_C 29.5, 24.2, 19.8, 14.1). Two additional carbons (δ_C 171.4 and 142.7) could be recognized by the strong HMBC correlations from the protons at δ_H 7.01, 2.50, 1.48 to δ_C 142.7 and the protons at δ_H 2.50 and 8.27 to δ_C 171.4.

These functionalities fulfilled the requisite hydrogen deficit, indicating **1** to be acyclic. Analysis of the ^{1}H-^{1}H COSY spectrum (Figure 2) revealed the spin systems H_3-1 (δ_H 1.33)/H-2 (δ_H 4.29), H-4 (δ_H 6.57)/H-5 (δ_H 7.01)/H-6

Table 1. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) Data of **1** and **2** in methanol-d_4 (δ in ppm)

No.	1			2	
	δ_H, mult. (*J* in Hz)	δ_C	δ_C (cal.)	δ_H	δ_C
1	1.33, d (6.9)	19.8, CH_3	19.4		172.6, C
2	4.29, q (6.9)	74.5, CH	73.1	5.72, s	120.2, CH
3		204.5, C	204.8		157.9, C
4	6.57, d (11.6)	126.5, CH	122.7	3.02, ddd (12.3, 8.3, 8.3); 2.45, ddd (12.3, 4.6, 4.6)	31.1, CH_2
5	7.01, dd (12.0, 11.6)	138.5, CH	142.4	1.80, m; 1.47, m	30.4, CH_2
6	8.27, d (12.0)	134.1, CH	135.5	3.28, dd (10.8, 1.8)	78.5, CH
7		142.7, C	145.4		73.6, CH
8	2.50, t (7.4)	29.5, CH_2	29.7	1.16, s	25.8, CH_3
9	1.48, m	24.2, CH_2	25.8	1.13, s	25.0, CH_3
10	0.93, t (7.2)	14.1, CH_3	13.2	1.86, s	24.8, CH_3
11		171.4, C	167.9		

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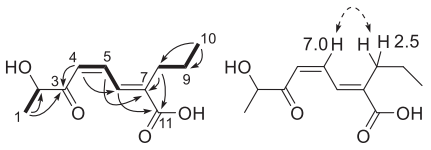

Figure 2. Key ^{1}H-^{1}H COSY (▬), HMBC (⤳), and NOESY correlations (⇢) of **1** and **2**

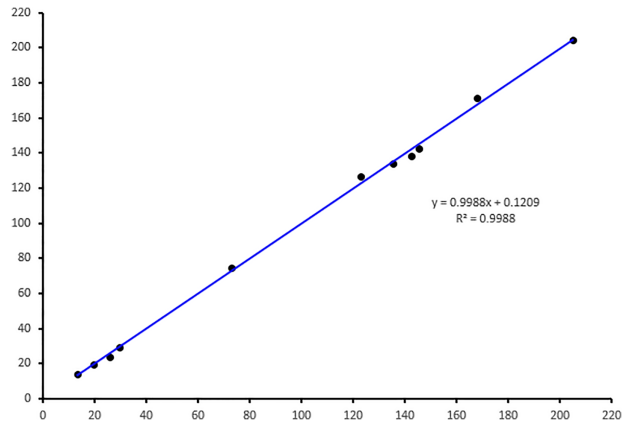

Figure 3. Regression analysis of experimental (x) and calculated ^{13}C NMR values (y) of **1**

(δ_H 8.27), and H_2-8 (δ_H 2.50)/H_2-9 (δ_H 1.48)/H_3-10 (δ_H 0.93), leading to the establishment of three fragments CH_3-CH(O), CH-CH-CH, and CH_2-CH_2-CH_3. The HMBC correlations (Figure 2) from H_3-1 (δ_H 1.33) to C-2 (δ_C 74.5), C-3 (δ_C 204.5), from H-4 (δ_H 6.57) to C-3, C-6 (δ_C 134.1), from H-5 (δ_H 7.01) to C-7 (δ_C 142.7), from H-6 (δ_H 8.27) to C-11 (δ_C 171.4), and from H_2-8 (δ_H 2.50) to C-7 (δ_C 142.7) and C-11 (δ_C 171.4) established the connectivity between the three fragments and other functional groups to give the gross structure. The configuration of the double bond Δ^4 in **1** was determined to be *cis* by the coupling constant (11.6 Hz), while the double bond Δ^6 was assigned to be *Z* configuration by the NOESY correlations between H-5 (δ_H 7.00) and H_2-8 (δ_H 2.50). The structure of **1** featured an extended conjugated system comprising a conjugated dienone moiety (Zhang et al., 2024; Chen et al., 2024; Wei et al., 2024) conjugated with a carboxylic acid group, which was rare in acyclic compound.

In order to determine the absolute configuration of the chiral center at C-2, the CD spectrum was recorded and was found to be a nearly horizontal line, and the optical rotation was about zero, these phenomena indicated the racemic nature of **1** (Sun et al., 2023; Li et al., 2023). A search of the SciFinder database revealed that the known structures exhibited marked differences from the proposed structure of **1**, precluding meaningful comparative analysis. Accordingly, the ^{13}C NMR calculations for compound **1** were carried out using the GIAO method at the mPW1PW91/6-311+G(d,p) level with the conductor-like polarizable continuum model (CPCM) in methanol-d_4 to validate its structure. The calculated ^{13}C NMR data (y) showed excellent agreement with the experimental values (x), as evidenced by an R^2 value of 0.9988 (Figure 3, Tables 1 and S1) (Yu et al., 2024). Thus, the structure was determined as shown and was named windienoic acid.

Compounds **3–5** were identified to be 6,7-dihydroxy-3,7-dimethyl-2-octenoic acid (**2**) (Wang et al., 2017), (−)-nortrachelogenin (**3**) (John & Tinto, 1992), (−)-trachelogenin (**4**) (Tang et al., 2022), and pinoresinol (**5**) (Serino et al., 2024) based on comparisons of the NMR data with those reported in the literature. The NMR data of compound **2** in the solvent methanol-d_4 was reported for the first time.

The inhibitory effects of these compounds against human lung cancer A549 cells were evaluated at 50 μM using the CCK-8 assay (Savaspun et al., 2024). Only compound **3** exhibited weak activity, with 57% inhibition, whereas the other compounds showed less than 30% inhibition. Consequently, the IC_{50} value of compound **3** was determined to be 42.3 μM, while the positive control doxorubicin had an IC_{50} value of 3.9 μM. The enhanced activity of 3 compared to its methylated derivative **4** suggested that the methoxy group substituted at the C-4 phenolic hydroxy plays a beneficial role in inhibitory potency.

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Author Contributions

Chunyan Wang: Writing–original draft, Investigation, Data curation.

Danhong Tao: Writing–review & editing, Data curation, Supervision, Project administration.

Availability of Data and Materials

Data and materials will be made available on request.

Ethics Approval

Not Applicable.

Conflicts of Interest

The authors declare that they do not have any conflict of interest.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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