ORIGINAL ARTICLE

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Rec. Nat. Prod. 17:5 (2023) 896-903

records of natural products

A New Lignan from the Leaves of *Piper sarmentosum*

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(Received June 12, 2023; Revised July 22, 2023; Accepted July 26, 2023)

Abstract: A new lignan, named 4′-methoxy-neotaiwanensol (**1**), together with five known compounds (**2**–**6**) were isolated from the leaves of the plant *Piper sarmentosum*. The known compounds consist of a phenylpropanoid (**2**), a flavonoid (**3**), two acyclic monoterpenoids (**4** and **5**), and a phenylacetic acid derivative (**6**). Structure elucidation of these compounds was conducted by detailed interpretation of the spectral data including NMR and HRESIMS data. Compounds **4** and **5** are new natural products and the NMR data in methanol-d_4 were reported for the first time. The other known compounds were elucidated to be hydroxychavicol (**2**), hispidulin (**3**), 4-hydroxy-benzeneacetic acid (**6**). In vitro, compounds **1** and **3** showed better inhibitory effects on α-glucosidase than the reference acarbose, and compound **1** and **2** exhibited moderate antioxidant effects.

Keywords: *Piper sarmentosum*; lignan; 4′-methoxy-neotaiwanensol; monoterpenoid.

1. Introduction

The genus *Piper*, belonging to the Piperaceae family, contains over 2000 species [1]. The studies on the chemical constituents of this genus resulted in various kinds of compounds including lignans, alkaloids, phenylpropanoids, terpenoids, etc.[1, 2] They exhibited various bioactivities, including antioxidative activity, cytotoxicity, anti-inflammation, and hepatoprotective. Some examples are as follows: bis-chavicol dodecanoyl ester and bis-hydroxychavicol dodecanoyl ester exhibited excellent antioxidant DPPH radical scavenging activity with IC_{50} values of 12.67 μg/mL and 1.08 μg/mL compared to ascorbic acid (IC_{50}:6.60 μg/mL) [3].

Piper sarmentosum is a perennial herb of Piperaceae. In China, it is distributed in Fujian, Guangdong, Guangxi, Yunnan, and Guizhou Provinces. And it also distributes widely in southeast Asian countries such as India, Vietnam, Malaysia, Philippines, and Indonesia. The root was used as a traditional Chinese medicine for the treatment of wind chill, cough and asthma, rheumatism, abdominal distension, and diarrhea. The leaves and stems can both be eaten raw or cooked.

Previous chemistry research of this plant led to the isolation of alkamides [4-6], lignans [5, 7], flavonoids and flavonoid glycosides [7], phenylpropanoid and phenylpropanoid glycosides [7], and four rare C-benzylated dihydroflavones [8]. Some compounds have significant biological activity. Some representative examples are as follows. Kadukoside had potent inhibitory effects against *Septoria tritici* with an IC_{50} value of 5.0 μM [7]. Pipercallosine could induce apoptosis in HT-29 cells via reducing the mitochondrial transmembrane potential moderately with ED_{50} values ranging from 1.6 to 13.6 μM. 7-Methoxydichamanetin and pinocembrin showed remarkable proteasome inhibitions with IC_{50} values of 3.45 and 2.87 μM, respectively. Bioassay study revealed that the extracts of *P. sarmentosum* showed extensive bioactivities including antimicrobial, antioxidant, anti-inflammatory, antihypertensive activities, anti-tumor, anti-osteoporosis, hypoglycemic, and insecticidal effects [7, 9].

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The article was published by ACG Publications
http://www.acgpubs.org/journal/records-of-natural-products September-October 2023 EISSN:1307-6167
DOI: http://doi.org/10.25135/rnp.407.2306.2811
Available online: August 22, 2023

In our study, the isolation, structural elucidation, and biological activity of a new lignan (**1**), two new natural acyclic monoterpenoids (**4** and **5**), and three known ones (**2**, **3,** and **6**) were presented (Figure 1).

2. Materials and Methods

2.1. General Experimental Procedures

Analytical reagents (petroleum ether, ethyl acetate, MeOH) and chromatographic grade reagents (MeOH and CH_3CN) were used. The UV data were obtained on a Cary 300 spectrometer. The ^1H NMR, ^{13}C NMR, and 2D NMR spectra were obtained on a Bruker Avance-400FT NMR spectrometer. The ESIMS spectrum was recorded on an AB SCIEX Triple TOF-4600 spectrometer. The isolation was performed on a HPLC equipped with a Shimadzu LC-6AD pump and a UV detector (absorptions at 254 and 210 nm were detected in this study). A YMC-Pack ODS-A column was used for separation.

2.2. Plant Materials

A sample of the leaves of *P. sarmentosum* was collected in Guangdong Province, China, in June 2021. The plant was identified by one of the authors Prof. Qian Chen. A voucher specimen was deposited in the Pharmacy for Chinese Medicine of the First People's Hospital of Linping District (Hangzhou, China) and was given the code number: 202106Pipersar.

2.3. Extraction and Isolation

The air-dried leaves of *P. sarmentosum* (1.0 kg) were powdered and extracted with 95% ethanol for three times at room temperature (r.t.) to afford a crude extract (98 g), which was suspended in water and partitioned with petroleum ether, EtOAc, and n-butanol to give the corresponding fractions.

The EtOAc extract (12 g) was fractionated into five subsequent fractions (F1–F5) by middle chromatogram isolated gel (MCI) using the eluent MeOH/H_2O (20:80→100:0). F2 was further separated into four subfractions F2a–F2d by an ODS silica gel using petroleum ether/ethyl acetate (5:1 to 1:1) as eluent. Compound **6** were obtained by further purification of F2a using a semi-preparative YMC-pack ODS-A column on HPLC with the solvent MeOH/H_2O (35:65, 2 mL/min). Fraction F2b was separated via HPLC eluting with ACN/H_2O (30:70, 2 mL/min) to obtain **2**. Fraction F2c was separated by HPLC using MeOH/H_2O (40:60) as eluent at a flow rate of 2 mL/min to afford **4** and **5**. Fraction F3 was split by an ODS silica gel to obtain five subfractions F3a–F3e, of which F3a was finally purified by HPLC using ACN/H_2O (45:55, 2 mL/min) to obtain **1** and **3.**

*4′-Methoxy-neotaiwanensol (**1**)*: Dark yellow oil; UV (MeOH) λ_{max} 209, 232, 283 nm; ^1H and ^{13}C NMR data, see Table 1; (–) HRESIMS m/z 311.1283 $[M - H]^-$, calcd for $C_{19}H_{19}O_4^-$, 311.1289.
Hydroxychavicol (**2**):δ_H 6.66 (1H, d, *J* = 8.0 Hz, H-5), 6.47 (1H, d, *J* = 8.0, 1.8 Hz, H-6), 6.60 (1H, d, *J* = 1.8 Hz, H-2), 3.20 (1H, d, *J* = 6.7 Hz, H-7), 5.90 (1H, dddd, *J* = 17.2, 10.2, 6.7, 6.7 Hz, H-8), 5.0 (1H, d, *J* = 17.2 Hz, H-9a); (1H, d, *J* = 10.2 Hz, H-9b).

*Hispidulin (**3**)*: 7.91 (2H, d, *J* = 7.7 Hz, H-2′,6′), 6.89 (2H, d, *J* = 7.7 Hz, H-3′,5′), 7.22 (1H, s, H-3), 7.21 (1H, s, H-8), 3.97 (3H, s, OCH_3).

*4-Hydroxy-benzeneacetic acid (**6**)*: 7.10 (2H, d, *J* = 8.0 Hz, H-2,6), 6.74 (2H, d, *J* = 8.0 Hz, H-3,5), 3.50 (2H, s, H_2-7).

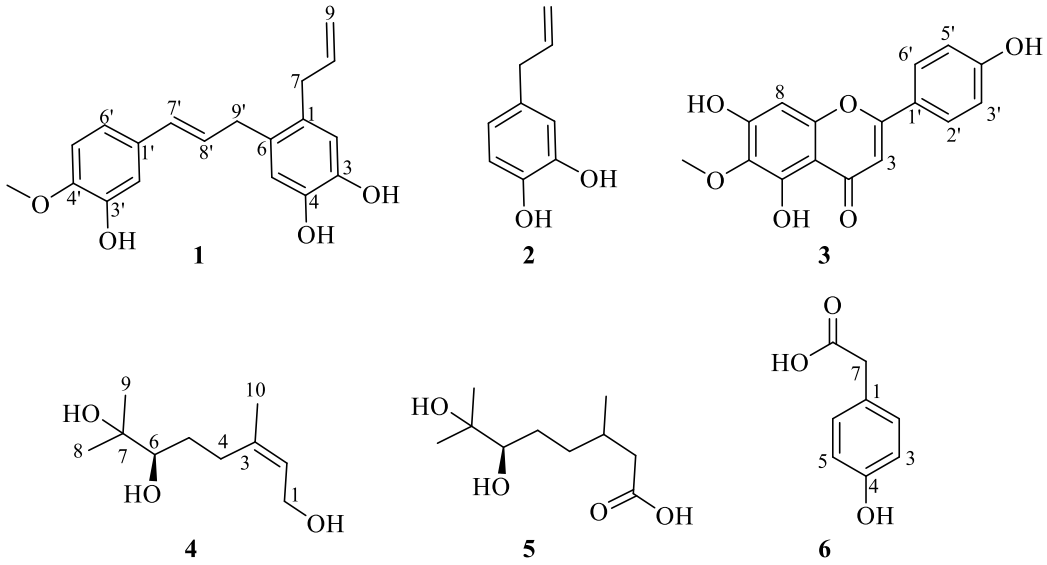

Figure 1. Structures of compounds **1**–**6** from the leaves of the plant *P. sarmentosum*

2.4. α-Glucosidase Inhibitory Assay

The *α*-glucosidase inhibitory activities were assayed according to the method reported [10-12]. The α-glucosidase (*Saccharomyes cerevisiae*) was diluted to the concentration of 0.2 U with a 0.1 M phosphate buffer (Na_2HPO_4 and NaH_2PO_4 at a pH of 6.8). The assay was conducted in a 200 μL reaction system comprising containing 98 μL of buffer, the *α*-glucosidase solution (25 μL) and 2 μL of samples (**1**–**6** dissolved in DMSO) or the solvent DMSO (Control). The solution was incubated followed by the addition of 25 μL of PNPG (0.4 mM). After incubation for 15 min at 37 ◦C, the reaction was quenched by adding 50 μL of sodium carbonate buffer (0.2 M). The optical density was recorded at the wavelength of 405 nm. The test was conducted in three replicates, acarbose was used as the positive control. The IC_{50} values are computed via concentration vs percent inhibition values. Inhibition was determined according to the following equation:

$$\text{Inhibition (\%)} = ((A_{Control} - A_{test})/A_{control})$$

2.5. Determination of Antioxidant Capacity

The procedure to determine the antioxidant effect was performed referring to that reported in the literature [13, 14]. The DPPH radical scavenging assay was conducted in 96-well microplates. 20 μL of compounds **1**–**6** in ethanol were added to 180 μL (150 μmol/L) DPPH solution. After avoiding light for 30 min, the absorbance at 517 nm was recorded using a microplate reader and the percentage of activity was calculated. The tests were performed in three replicates, and vitamin C was used as a positive control. The IC_{50} values is calculated by plotting inhibition percentage against the concentrationThe DPPH scavenging activity was calculated according to the following equation:

$$\text{Scavenging activity (\%)} = [A_{solvent} - A_{sample}]/A_{solvent} \times 100\%.$$

3. Results and Discussion

3.1. Structure Elucidation

Compound **1** had a molecular formula of $C_{19}H_{20}O_4$ as assigned by the HRESIMS data (m/z 311.1283 $[M - H]^-$, calcd for $C_{19}H_{19}O_4^-$ 311.1289) and ^{13}C NMR spectroscopy, suggesting ten indexes of hydrogen deficiency. The total integrals of the protons from the ^1H NMR in methanol-d_4 were 17, suggesting the presence of three hydroxy groups. The ^1H NMR spectrum (Table 1) exhibited a 1,2,4-trisubstituted benzene moiety [δ_H 6.83 (1H, d, J = 1.6 Hz); 6.82 (1H, d, J = 1.6 Hz); 6.74 (1H, dd, J = 8.4, 1.6 Hz)], a 1,2,4,5-tetrasubstituted benzene moiety [δ_H 6.63 (1H, s); 6.59 (1H, s)], two coupled olefinic protons [δ_H 6.19 (1H, d, J = 16 Hz); 6.11 (1H, dt, J = 16.0, 6.0, 6.0 Hz)] for a double bond, three olefinic protons for a terminal double bond [δ_H 5.93 (1H, ddt, J = 18.7, 11.2, 6.2 Hz); 4.95 (1H, d, J = 18.7 Hz); 5.00 (1H, d, J = 11.2 Hz)], two sets of doublet each integrated for two protons for two methylenes [δ_H 3.34 (2H, d, J = 6.0 Hz), 3.27 (2H, d, J = 6.2 Hz)], and a methoxy [δ_H 3.82 (3H, s)]. The ^{13}C NMR (Table 1) and HSQC spectra indicated the presence of sixteen aromatic carbons including eight methines (δ_C 112.7, 113.4, 117.8, 117.9, 119.2, 128.6, 131.3, 139.0), four oxygenated non-hydrogenated aromatic carbons (δ_C 144.5×2, 147.5, 148.4), two quaternary carbons (δ_C 130.8, 132.7), a methylene (δ_C 115.3), as well as two methyene carbons (δ_C 37.5, 115.3), and a methoxy carbon (δ_C 56.4). The functional groups including two benzene moieties and two double bonds were accounted for all ten indexes of hydrogen deficiency, suggesting the absence of additional ring in the structure. The gross structure of **1** was determined via interpretation of 2D NMR analyses (Figure 2).

Table 1. ^1H and ^{13}C NMR Data of **1** in Methanol-d_4[a]

No.	**1**		**Neotaiwanensol** [15, 16]	
	δ_H	δ_C	δ_H	δ_C
1		130.8, C		130.5
2	6.63, s	117.8, CH	6.65, s	118.2
3		144.5, C		144.8
4		144.5, C		144.8
5	6.59, s	117.9, CH	6.68, s	118.1
6		130.4, C		131.2
7	3.27, d (6.2)	37.5, CH_2	3.29, dt (6.4, 1.5)	37.8
8	5.93, ddd (18.7, 11.2, 6.2)	139.2, CH	5.93, ddt (17.6, 9.6, 6.4)	139.6
9	4.95, d (18.7), 5.00, d (11.2)	115.3, CH_2	4.99, m	115.9
1′		132.7, C		131.7
2′	6.83, d (1.6)	113.4, CH	6.90, d (1.8)	114.1
3′		147.5, C		146.4
4′		148.4, C		146.1
5′	6.82, d (8.4)	112.7, CH	6.74, d (8.2)	116.7
6′	6.74, dd (8.4, 1.6)	119.2, CH	6.71, dd (8.2, 1.8)	119.8
7′	6.19, d (16)	131.3, CH	6.25, dt (15.6, 1.3)	131.8
8′	6.11, dt (16.0, 6.0, 6.0)	128.6, CH	6.10, dt (15.6, 6.5)	128.1
9′	3.34, d (6.0)	36.5, CH_2	3.35, dt (6.5, 1.3)	36.7
OCH_3	3.82, s	56.4, OCH_3		

[a] ^1H NMR (400 MHz); ^{13}C NMR (100 MHz)

The COSY relationship between the methylene protons [δ_H 3.27, (2H, d, J = 6.2 Hz)] and the protons for the terminal double bond [δ_H 5.00 (1H, d, J = 11.2 Hz); 4.95 (δ_H 1H, d, J = 18.7 Hz)] in combination with HMBC correlations from H_2-7 [δ_H 3.27 (2H, d, J = 6.2 Hz)] to C-1 (δ_C 130.8), C-2 (δ_C 117.8), C-6 (δ_C 130.4) led to the construction of a hydroxychavicol moiety. Additional HMBC

correlations from H-7′ (δ_H 6.19) to C-1′ (δ_C 132.7), C-2′ (δ_C 113.4), and C-6′ (δ_C 119.2), and from the methoxy protons at δ_H 3.82 to C-4′ (δ_C 148.4) established the isochavibetol unit. The above two fragments were linked together via the C-6–C-9′ bond that was evidenced by the HMBC correlations from H-9′ (δ_H 3.34) to C-1 (δ_C 130.8), C-5 (δ_C 117.9), and C-6 (δ_C 130.4). The *E* geometry of the double bond Δ7′ was assigned based on the large coupling constant $J_{H\text{-}7'\text{-}H\text{-}8'}$ (16.0 Hz). The other three oxygenated non-hydrogenated carbons were linked to hydroxyl groups according to the molecular formula. Thus, the structure of **1** was established as shown in figure 1. Compound **1** was found to be 4′-methoxy derivative of the known compound neotaiwanensol and was named to be 4′-methoxy-neotaiwanensol accordingly [15, 16].

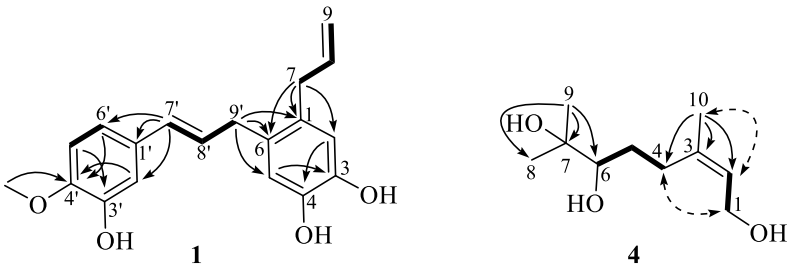

Figure 2. Selected HMBC (⟶), COSY (—), and NOESY (⇠⇢) correlations of **1** and **4**

Compound **4** and **5** were structurally related monoterpenoid derivatives. The ^{1}H NMR spectrum (Table 2) of **4** exhibited two tertiary methyl singlets [δ_H 1.15 (3H, s), 1.11 (3H, s)], an olefinic methyl [δ_H 1.74 (3H, s)], an oxygen-bearing proton [δ_H 3.20 (1H, dd, J = 10.8, 1.6 Hz)], an olefinic triplet [δ_H 5.40 (1H, t, J = 6.9 Hz)], two methyenes [δ_H 2.24 (2H, m); 1.35 (2H, m], and an oxygenated methylene [δ_H 4.08 (2H, d, J = 6.9 Hz)]. The ^{13}C NMR and HSQC spectra revealed the presence of 10 carbons (Table 2), which consist of three methyl carbons (δ_C 25.6, 24.6, 23.4), three oxygenated methylene carbons including one oxygenated one (δ_C 58.9, 30.2, 29.6), one oxygenated sp^3 methine (δ_C 78.5), one oxygenated non-hydrogenated carbon (δ_C 73.6), and a trisubstituted double bond (δ_C 139.9, 125.7). The ^{1}H-^{1}H COSY correlations from H_2-5 (δ_H 1.35) to H_2-4 (δ_H 2.24) and H_2-6 (δ_H 3.20) as well as between H_2-1 (δ_H 4.08) and H-2 (δ_H 5.10), in association with the HMBC correlations from H_3-9 (δ_H 1.15) to C-6 (δ_C 78.5), C-7 (δ_C 73.6), C-8 (δ_C 25.6), and from H_3-8 (δ_H 1.11) to C-2 (δ_C 5.40), C-3 (δ_C 139.9), C-4 (δ_C 30.2) assembled these functional groups to give the structure of **4** (Figure 2). The *E*-configured double bond Δ^2 was assigned by the NOESY correlations of H_3-10 (δ_H 1.74)/H-2 (δ_H 5.40) and H_2-1 (δ_H 4.08)/H_2-4 (δ_H 2.24). The absolute configuration of the asymmetric center C-6 was assigned as *R* by comparing its specific rotation ($[\alpha]_D^{25}$ +42) with those of the synthetic products (*R*: $[\alpha]_{20}^D$ =+38.8; *S*: $[\alpha]_{20}^D$ = –39.3) [17]. Thus, compound **4** was determined to be (2*Z*, 6*R*)-3,7-dimethyl-2-octene-1,6,7-triol (**4a**). The ^{1}H NMR and ^{13}C NMR of **5** were very similar to those of **4**, the obvious differences were owing to the presence of a carboxyl carbon (δ_C 177.4), an additional methylene (δ_C 42.6), and a sp^3 methine (δ_C 31.6) instead of the oxygenated methylene (δ_C 58.9) and the double bond (δ_C 139.9, 125.7), suggesting that the double bond was hydrogenated and the oxygenated methylene was oxidized to carboxyl carbon. The structure of **5** was finally determined by comparing its NMR data with the reported synthetic product (6*R*)-6,7-dihydroxycitronellic acid (**5a**) [18]. Compounds **4** and **5** were reported for the first time from nature.

Table 2. ^{1}H and ^{13}C NMR Data of **4–5** in Methanol-d_4[a]

No.	**4**		**4a** [b]	**5**		**5a** [c]
	δ_H	δ_C		δ_H	δ_C	
1	4.08, d (6.9)	58.9	57.5	2.06, dd (14.6, 8.4)	177.4	174.5
2	5.40, t (6.9)	125.7	124.2	2.32, dd (14.6, 5.7)	42.6	42.5
3		139.9	140.5	1.94, m	31.6	30.1
4	2.24, m	30.2	28.0	1.24, m	35.1	33.9
5	1.35, m	29.6	27.1	1.65, m	29.4	28.2
6	3.20, dd (10.8, 1.6)	78.5	75.5	3.20, m	79.6	77.7
7		73.6	72.3		73.6	71.6
8	1.11, s	25.6	25.9	1.12, s	25.6	26.3
9	1.15, s	24.6	22.8	1.15, s	24.6	24.5
10	1.74, s	23.4	22.2	0.97, d (6.6)	20.2	20.0

[a] ^{1}H NMR (400 MHz); ^{13}C NMR (100 MHz); [b] $CDCl_3$; [c] DMSO-d_6

Besides, the other known compounds were assigned to be hydroxychavicol (**2**)[19], hispidulin (**3**) [20], and 4-hydroxy-benzeneacetic acid (**6**) [21] by comparing the ^{1}H NMR data with those reported in the literature.

In the current work, a new lignan (**1**), a known phenylpropanoid (**2**), a known flavonoid (**3**), two new acyclic monoterpenoids (**4** and **5**), and a known phenylacetic acid derivative (**6**) were obtained. Compound **1** was methoxylated derivative of neotaiwanensol, a lignan previously isolated from *P. taiwanense* and *P. betle*. Hydroxychavicol (**2**) was reported from several *Piper* species including P. kadsura and *P. betle* [22, 23]. Compounds **3–5** was reported from this genus for the first time, particularly, compounds **4** and **5** were new natural products. Phenylpropanoids and lignans were the most common compounds isolated from this genus and are considered to be chemotaxonomic markers of this genus [24].

*3.2. The Antioxidant Capacity and α-Glucosidase Inhibitory Activity of the Compounds **1**–**6***

All compounds were firstly tested for their inhibitions on α-glucosidase at an initial concentration of 500 μM and antioxidant activity at 50 μM. As results, compounds **1** and **3** exhibited inhibitory activity on α-glucosidase and **1** and **2** showed antioxidant activity. They were further assessed to determine the IC_{50} values. Compounds **1** and **3** obviously inhibited α-glucosidase with IC_{50} values of 213 and 279 μM (the positive control acarbose, 507 μM). Compound **1** and **2** showed moderate antioxidant activity with IC_{50} values of 18.6 μM for **1** and 25.1 μM for **2** (the positive control vitamin C 16.7 μM). While other compounds revealed ignorable effects at the initial screening concentration.

Supporting Information

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

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