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Lignans and Other Compounds From the Roots of *Pandanus tonkinensis* and Their Lipid Peroxidation Inhibitory Activity

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Abstract

A new phenylpropane (**1**) and 9 known (**2**-**10**) compounds were isolated from the methanol extract of *Pandanus tonkinensis* roots. Their chemical structures were determined as (7*S*)-2,6-dimethoxyphenyl-7,9-propanediol-1-*O*-*β*-D-glucopyranoside (**1**), isorhapontigenin (**2**), pinoresinol-4,4′-di-*O*-*β*-D-glucoside (**3**), isoeucommin A (**4**), pinoresinol-4′-*O*-*β*-D-glucoside (**5**), acanthoside B (**6**), eucommin A (**7**), urolignoside (**8**), benzyl *O*-*α*-L-arabinopyranosyl-(1→6)-*β*-D-glucopyranoside (**9**), and (6*S*,9*S*)-roseoside (**10**) by comprehensive analysis of high-resolution electron spray ionization mass spectrum and nuclear magnetic resonance spectral data, as well as by comparison of their spectral data with those reported in the literature. In addition, the stereochemistry of **1** was successfully determined by both theoretical and calculated CD spectra. All the isolates were tested for their lipid peroxidation inhibitory effects by *in vitro* assay. Compounds **2**-**7** exhibited significantly lipid peroxidation inhibitory effects with IC_{50} values of 21.3 ± 1.7, 61.9 ± 3.9, 57.5 ± 5.5, 10.4 ± 0.7, 28.9 ± 0.3, 54.2 ± 3.5 μM, respectively, compared to that of the positive control, trolox (31.4 ± 2.2 μM).

Keywords

Pandanus tonkinensis, pandanaceae, phenylpropanoid, lignan, lipid peroxidation inhibitory

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Introduction

The plant *Pandanus tonkinensis* Mart. ex B. Stone belongs to Pandanaceae family, which is widely distributed in the northern provinces of Vietnam, such as Hoa Binh, Vinh Phuc, Bac Giang, and Ninh Binh, and is used in folk medicine to treat liver diseases very effectively.[1,2] However, up to now, there has been no publication on the chemical composition of this plant. In the program to search for antioxidant components from Vietnamese medicinal plants, the roots of *P tonkinensis* were selected for research. This paper reports the isolation and structure determination of 1 new and 9 known compounds from the methanol extract of the roots of this plant. In addition, the lipid peroxidation inhibitory effects of the isolated compounds were also evaluated by *in vitro* assay.

Results and Discussion

Compound **1** (Figure 1) was obtained as a white amorphous powder. Its molecular formula was determined to be $C_{17}H_{26}O_9$ from the pseudo-molecular ion peaks at *m/z* 397.1470 $[M+Na]^+$ (calcd. for $[C_{17}H_{26}O_9Na]^+$, 397.1469, $\Delta = +0.2$ ppm), and *m/z* 392.1910 $[M+NH_4]^+$ (calcd. for $[C_{17}H_{30}O_9N]^+$, 392.1915, $\Delta = -1.2$ ppm) in the high-resolution electron spray ionization mass spectrum (HRESIMS), indicating 5 degrees of unsaturation. The ^{1}H nuclear magnetic resonance (NMR) spectrum of **1** exhibited 2 aromatic protons at δ_H 6.71 (2H, s)

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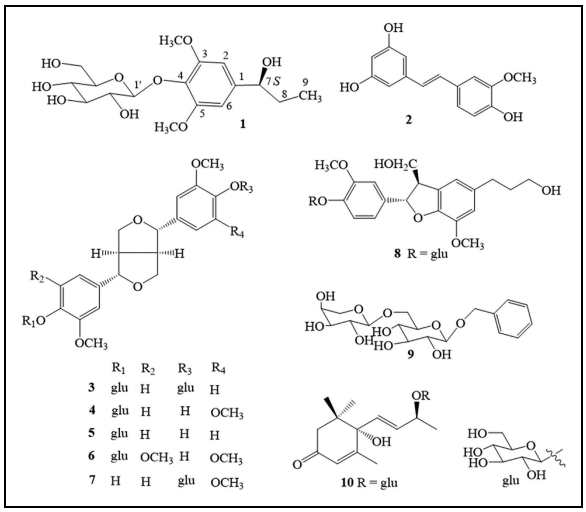

Figure 1. Chemical structures of compounds **1-10**.

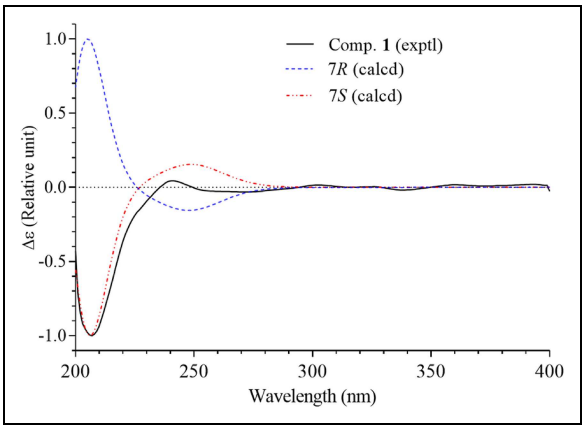

Figure 2. Theoretical calculated ECD spectra of 2 possible stereoisomers and experimental CD for compound **1**.

suggesting a 1,3,4,5-substituted symmetrical aromatic ring, one methyl doublet signal at δ_H 0.94 (3H, d, $J = 7.2$ Hz), 2 methoxy groups at δ_H 3.89 (6H, s), and an anomeric proton at δ_H 4.85 (1H, d, $J = 7.8$ Hz). The ^{13}C NMR and HSQC spectra of **1** showed signals of 17 carbon atoms, including 4 nonprotonated, 8 methines, 2 methylenes, and 3 methyls. Of these, 6 carbon signals (δ_C 105.6, 75.8, 77.8, 71.4, 78.3, and 62.6) were assigned to a glucopyranosyl group. The above evidence suggested that **1** was a phenylpropane glycoside having 2 methoxy groups at C-3 and C-5 of the aromatic ring.[3] In the propane side chain, the observed HSQC correlations of H-7 (δ_H 4.51)/C-7 (δ_C 76.6), H-8 (δ_H 1.76)/C-8 (δ_C 30.0), and H-9 (δ_H 0.94)/C-9 (δ_C 10.6), as well as the proton and carbon chemical shifts, the multiplets, and ^1H-^1H coupling constants indicated the presence of a -CH(OH)-CH_2-CH_3 moiety.[3] In the HMBC spectrum of **1**, H-8 correlated to C-1 (δ_C 143.4)/C-2 and C-5 (δ_C 105.0), methoxy protons (δ_H 3.89) correlated to C-3/C-5 (δ_C 154.1), and the anomeric proton (H-1′, δ_H 4.85) correlated to C-4 (δ_C 135.3) (Supplemental Figures S1). This evidence confirmed the propane moiety attached to C-1, 2 methoxy groups linked to C-3 and C-5, and the glucose attached to C-4. Furthermore, the coupling constant of the anomeric proton, $J_{H\text{-}1'/H\text{-}2'} = 7.8$ Hz, indicated a *β*-glucopyranosyl linkage. Later, the presence of a D-glucose moiety was identified by acid hydrolysis, treatment with cysteine methyl ester and *O*-tolyl isothiocyanate, followed by HPLC analysis and comparison with the t_R values of authentic D/L-glucose.[4] All the above evidence corresponded to that of (7*R*)-2,6-dimethoxyphenyl-7,9-propanediol-1-*O*-*β*-D-glucopyranoside.[4] However, the optical rotation of **1** ($[\alpha]_D^2$3: + 9.0) differed from that of (7*R*)-2,6-dimethoxyphenyl-7,9-propanediol-1-*O*-*β*-D-glucopyranoside ($[\alpha]_D^{23}$: - 10.0)[3] suggesting a (7*S*)-configuration of **1**. This suggestion was confirmed based on both theoretical and calculated CD spectra. The 2 possible configurations 7*S*/7*R* of **1** were submitted for calculation of their theoretical ECD spectra and compared with experimental results (Figure 2). The experimental CD analysis of **1** was in good agreements with the 7*S*-configuration. Consequently, the complete structure of compound **1** was elucidated as (7*S*)-2,6-dimethoxyphenyl-7,9-propanediol-1-*O*-*β*-D-glucopyranoside (Supplemental Figures S2-S7).

The other compounds were identified as isorhapontigenin (**2**),[5] pinoresinol-4,4′-di-*O*-*β*-D-glucoside (**3**),[6] isoeucommin A (**4**),[7] pinoresinol-4′-*O*-*β*-D-glucoside (**5**),[8] acanthoside B (**6**),[9] eucommin A (**7**),[10] urolignoside (**8**),[11,12] benzyl *O*-*α*-L-arabinopyranosyl-(1→6)-*β*-D-glucopyranoside (**9**),[13] and (6*S*,9*S*)-roseoside (**10**)[14] by comparisons of their NMR spectroscopic data with those reported in the literature (Supplemental Figures S8-S43). Furthermore, the (6*S*,9*S*)-configuration of **10** was determined based on the positive Cotton effect at 240 nm in its CD spectrum and the lower carbon chemical shift of C-9 (δ_C 74.6 ppm).[14]

Phenolic compounds, including lignans, are a type of secondary plant metabolite exhibiting diverse structures, which exhibit potentially beneficial bioactive properties due to antioxidant activity.[15–18] Therefore, all the isolates were tested for their lipid peroxidation inhibitory effects by *in vitro* assay.[19,20] At a concentration as high as 100 μg/mL, compounds **2**-**7** exhibited significantly lipid peroxidation inhibitory effects with inhibition in the range from 72.7% to 88.4%, compared to the positive control, trolox, 87.1%, whereas compounds **1**, and **8**-**10** showed no activity (Supplemental Table S1). Further evaluation of their lipid peroxidation inhibitory effects showed that compounds **2**-**7** exhibited significant lipid peroxidation inhibitory effects with IC_{50} values of 21.3 ± 1.7, 61.9 ± 3.9, 57.5 ± 5.5, 10.4 ± 0.7, 28.9 ± 0.3, 54.2 ± 3.5 μM, respectively, compared to that of the positive control, trolox (31.4 ± 2.2 μM). Regarding structure activity relationship, our results suggested that the lignan glycoside compounds having a furofuran structure showed the most lipid peroxidation inhibitory effects (Table 1).

Materials and Methods

General Experimental Procedures

Optical rotation was measured on a Jasco P-2000 polarimeter, IR spectra on a Spectrum Two FT-IR spectrometer, CD

Table 1. Lipid Peroxidation Inhibitory Activity of Compounds **1**-**10**.

Compounds	IC_{50} (μM)	Compounds	IC_{50} (μM)
1	>100	**6**	28.9 ± 0.3
2	21.3 ± 1.7	**7**	54.2 ± 3.5
3	61.9 ± 3.9	**8**	>100
4	57.5 ± 5.5	**9**	>100
5	10.4 ± 0.7	**10**	>100
Trolox[a]	31.4 ± 2.2		

[a]Positive control.

spectra on a Chirascan spectrometer (Applied Photophysics), NMR spectra on a Bruker Avance NEO 600 MHz spectrometer, and HRESIMS on a SCIEX X500 QTOF LC/MS. Flash column chromatography was performed using either silica gel or reversed phase (RP-18) resins as adsorbent. The ratio between the amount of silica gel and fraction was 20/1 (w/w). A fraction collector was set by volume per tube (15 mL/tube). Fractionation was monitored by thin layer chromatography (TLC). Contents of test tubes showing a similar TLC pattern were combined. TLC was carried out on either precoated silica gel 60 F_{254} and/or RP-18 F_{254S} plates. Compounds were visualized by UV irradiation (254 and 365 nm) and by spraying with H_2SO_4 solution (5%), followed by heating with a heat gun. HPLC was conducted on an Agilent 1100 system including quaternary pump, autosampler, DAD detector, and preparative HPLC column YMC J'sphere ODS-H80 (4 μm, 20 × 250 mm). An isocratic mobile phase with a flow rate of 3 mL/min was used in pre-HPLC.

Plant Material

The roots of *Pandanus tonkinensis* Mart. ex B. Stone were collected in Son Duong District, Hoa Binh Province, Vietnam, in April 2021, and identified by Dr Do Thi Xuyen, Head of Department of Botanic, Faculty of Biology, VNU University of Science. A voucher specimen (code HNU 024663) is kept at the Herbarium, Vietnam National University, Hanoi, Vietnam.

Extraction and Isolation

Dried powder of *P tonkinensis* roots (14 kg) was sonicated with methanol (3 times, each 25 L MeOH). After removal of solvent, the MeOH extract (40 g) was suspended in water and then partitioned with *n*-hexane, dichloromethane, and ethyl acetate to give the corresponding residues (PT1, 2.5 g, PT2, 3.7 g, PT3, 5.3 g), and water (PT4, 27.0 g). After checking by TLC, PT4 (26.5 g) was further chromatographed on a Diaion HP-20 column eluting with water to remove sugar, then with increasing concentration of methanol in water (25, 50, and 100%) to obtain 3 fractions, PT4A (2.4 g), PT4B (2.6 g), and PT4C (21.0 g). PT4C (20.0 g) was chromatographed on a silica gel column eluting with dichloromethane/methanol (v/v) 20:1, 5:1, 1:1, and 0:1 (each 2 L) to give 4 corresponding subfractions (PT4C1-PT4C4). PT4C1 (14.0 g) was further chromatographed on a YMC column eluting with acetone/water (1/3, v/v) to give 7 smaller fractions, PT5A-PT5G. PT5C (5.8 g) was fractionated by silica gel CC eluting with dichloromethane/methanol (7/1, v/v) to obtain 6 subfractions, PT6A-PT6F. PT6A (83.0 mg) was chromatographed by HPLC (J'sphere H-80 column, 250 mm length × 20 mm ID, eluting with 15% acetonitrile in water, a flow rate of 2.5 mL/min) to give compounds **1** (t_R 30.689, 8.7 mg) and **10** (t_R 35.024, 20.2 mg). PT6D (172.6 mg) was separated by HPLC (J'sphere H-80 column, 250 mm length × 20 mm ID, eluting with 13% acetonitrile in water, a flow rate of 2.5 mL/min) to give compound **9** (t_R 37.50, 36.0 mg). PT6E (151.3 mg) was chromatographed by HPLC (J'sphere H-80 column, 250 mm length × 20 mm ID, eluting with 15% acetonitrile in water, a flow rate of 2.5 mL/min) to give compounds **2** (t_R 35.240, 6.0 mg) and **3** (t_R 40.158, 16.4 mg). Fraction PT5F (1.4 g) was separated by silica gel CC eluting with dichloromethane/methanol (10/1, v/v) to give 6 smaller fractions, PT7A-PT7F. PT7A (93.9 mg) was chromatographed by HPLC (J'sphere H-80 column, 250 mm length × 20 mm ID, eluting with 20% acetonitrile in water, a flow rate of 2.5 mL/min) to give compounds **4** (t_R 48.319, 4.9 mg), **5** (t_R 50.933, 40.4 mg), **6** (t_R 53.606, 9.6 mg), and **7** (t_R 57.438, 4.5 mg). PT7E (17.8 mg) was chromatographed by HPLC using the same conditions to give compound **8** (t_R 24.60, 4.1 mg).

(7S)-2,6-Dimethoxyphenyl-7,9-Propanediol-1-O-β-D-Glucopyranoside (1). Colorless amorphous powder, $[\alpha]_D^{25}$: + 9.0 (*c* 0.1, MeOH); IR (KBr) ν_{max}: 3428, 2935, 1650, 1078 $cm^{-}1$. HRESIMS *m/z* 397.1470 $[M + Na]^+$ (calcd. for $[C_{17}H_{26}O_9Na]^+$, 397.1469, Δ = + 0.2 ppm) and *m/z* 392.1910 $[M + NH_4]^+$ (calcd. for $[C_{17}H_{30}O_9N]^+$, 392.1915, Δ = - 1.2 ppm).

^{1}H NMR (CD_3OD, 600 MHz) δ (ppm): 6.71 (2H, s, H-2, H-6), 4.51 (1H, t, *J* = 7.2 Hz, H-7), 1.76 (2H, m, H-8), 0.94 (3H, d, *J* = 7.2 Hz, H-9), 4.85 (1H, d, *J* = 7.8 Hz, H-1′), 3.50 (1H, dd, *J* = 9.0, 7.8 Hz, H-2′), 3.43 (1H, dd, *J* = 9.0, 9.0 Hz, H-3′), 3.44 (1H, dd, *J* = 9.0, 9.0 Hz, H-4′), 3.22 (1H, m, H-5′), 3.68 (1H, dd, *J* = 12.0, 5.0 Hz, H_a-6′), 3.79 (1H, dd, *J* = 12.0, 5.0 Hz, H_b-6′), 3.89 (6H, s, 2 × OCH_3). ^{13}C NMR (CD_3OD, 150 MHz) δ (ppm): 143.4 (C-1), 105.0 (C-2, C-6), 154.1 (C-3, C-5), 135.3 (C-4), 76.6 (C-7), 30.0 (C-8), 10.6 (C-9), 105.6 (C-1′), 75.8 (C-2′), 77.8 (C-3′), 71.4 (C-4′), 78.3 (C-5′), 62.6 (C-6′), 57.0 (2 × OCH_3).

Acid Hydrolysis of Compound 1. Compound **1** (1.5 mg) was treated with 2 N aqueous HCl (2 mL) in sealed flask at 90 °C for 2 h. The acidic aqueous mixture was dried, $CHCl_3$ (1 mL) was added, and the $CHCl_3$ solution was extracted with H_2O (1 mL). The aqueous fraction was evaporated to dryness to obtain the liberated sugar. Sugar samples, including the saccharide hydrolysis product of **1**, D-glucose and L-glucose (Sigma Aldrich) were separately dissolved in 1 mL pyridine and heated with 2 mg L-cysteine methyl ester at 60 °C for 1 h,

and then 2.5 μL *O*-tolyl isothiocyanate was added to the reaction mixture and further reacted at 60 °C for 1 h. Then, the reaction mixture was analyzed on a 250 × 4.6 mm i.d. Ultimate™ XB-C18 column (Welch Material, Inc.) at 35 °C with isocratic elution with 25% CH_3CN in 0.5% formic acid for 40 min at a flow rate of 0.8 mL/min, and detection with an UV detector (at 250 nm). Under these conditions, the standard sugars gave peaks at t_R (min) 22.0 and 23.0 for L-glucose and D-glucose, respectively. A peak at t_R (min) 23.0 (D-glucose) for **1** was observed.

Antioxidant TBARS assay[19,20]

Thiobarbituric acid reactive substances (TBARS) assay values are usually reported in MDA equivalents, a compound formed from the decomposition of polyunsaturated fatty acid lipid peroxides. Briefly, a 0.1 mL sample at difference doses was added to 1 mL of mice brain homogenate (10%) and 0.8 mL phosphate buffer in the presence of 0.1 mL Fenton reagent ($FeSO_4$ 0.1 mM: H_2O_2 15 mM at a ratio of 1:1). After incubating the mixture at 37 °C for 15 min, 1 mL of trichloroacetic acid 10% was added to each tube and the tubes were centrifuged at 12000 rpm for 5 min. The supernatant was then mixed with 1 mL of 0.8% thiobarbituric acid at a ratio of 2:1 and heated at 100 °C for 15 min. After cooling, the absorbance of the mixture was determined at 532 nm by using a microplate reader (BioRad). The percentage inhibition was calculated by the following formula:

$$\%\ \text{Inhibition of lipid peroxidation} = \left[\frac{(OD_{control} - OD_{sample})}{OD_{control}}\right] \times 100$$

Conclusions

Phytochemical study of the methanol extract of *P tonkinensis* roots led to the isolation of a new phenyl propane, (7*S*)-2,6-dimethoxyphenyl-7,9-propanediol-1-*O*-*β*-D-glucopyranoside (**1**), and 9 known (**2**-**10**) compounds. The chemical structure of these compounds were determined by comprehensive analysis of HRESIMS and NMR spectral data, as well as by comparison of their spectral data with those reported in the literature. The stereochemistry of **1** was successfully determined by both theoretical and calculated CD spectra. Compounds **2**-**7** exhibited significant lipid peroxidation inhibitory effects in an *in vitro* antioxidant TBARS assay with IC_{50} values of 21.3 ± 1.7, 61.9 ± 3.9, 57.5 ± 5.5, 10.4 ± 0.7, 28.9 ± 0.3, 54.2 ± 3.5 μM, respectively, compared to that of the positive control, trolox, (31.4 ± 2.2 μM).

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Author Contribution

Research idea: PH Viet, DH Anh, NX Nhiem, PV Kiem. Isolation: DTH Trang. Structure elucidation and writing: BH Tai, DTH Trang, DH Anh, PV Kiem.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. GQ3

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Supplemental material

Supplemental material for this article is available online.

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List of Abbreviations

NMR	nuclear magnetic resonance
COSY	correlation spectroscopy
HRESIMS	high-resolution electrospray ionization mass spectrometry
HMBC	heteronuclear multiple bond correlation
HSQC	heteronuclear single quantum coherence
NOESY	nuclear overhauser effect spectroscopy
ECD	electronic circular dichroism
TBARS	thiobarbituric acid reactive substances
MDA	malonyl dialdehyde