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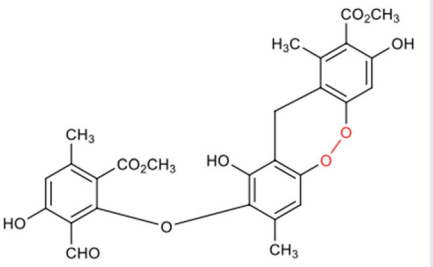
Paresordin A, a new diphenyl cyclic peroxide from the lichen *Parmotrema praesorediosum*

Bui Linh Chi Huynh[a], Nguyen Kim Tuyen Pham[b] and Tan Phat Nguyen[c,d]

[a]Department of Science, Dong Nai University, 04 Le Quy Don, Bien Hoa City, Dong Nai Province 760000, Vietnam; [b]Faculty of Environmental Science, Sai Gon University, 273 An Duong Vuong, Ho Chi Minh City 700000, Vietnam; [c]Faculty of Chemistry, Graduate University of Science and Technology, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Hanoi 100000, Vietnam; [d]Bioactive Compounds Laboratory, Institute of Chemical Technology, Vietnam Academy of Science and Technology, 1A Thanh Loc 29, Thanh Loc, District 12, Ho Chi Minh City 700000, Vietnam

ABSTRACT

From the lichen Parmotrema praesorediosum, one new diphenyl peroxide, named praesordin A (1), together with four depsidones, including virensic acid (**2**), protocetraric acid (**3**), 8′-*O*-methylprotocetraric acid (**4**), and furfuric acid (**5**) were purified. Their structures were chacracterized using extensive HR-ESI-MS and NMR spectroscopic methods. The isolated compounds (**2-5**) possessed stronger α-glucosidase inhibitory activity (IC_{50} = 43.7-110.1 μM) than the standard drug acarbose (IC_{50} = 214.5 μM).



Praesordin A (1)

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1. Introduction

The *Parmotrema* (Parmeliaceae) is a large genus with approximately 350 species of foliose lichens and a high level of diversity in the tropical areas of the world. Phytochemical studies evidenced γ-lactone acids as the main component of *P. praesorediosum* [1–3]. Further, our previous papers evinced diphenyl ethers were

CONTACT Tan Phat Nguyen ntphat@ict.vast.vn; hainhanchi@yahoo.com.vn Faculty of Chemistry, Graduate University of Science and Technology, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Hanoi 100000, Vietnam

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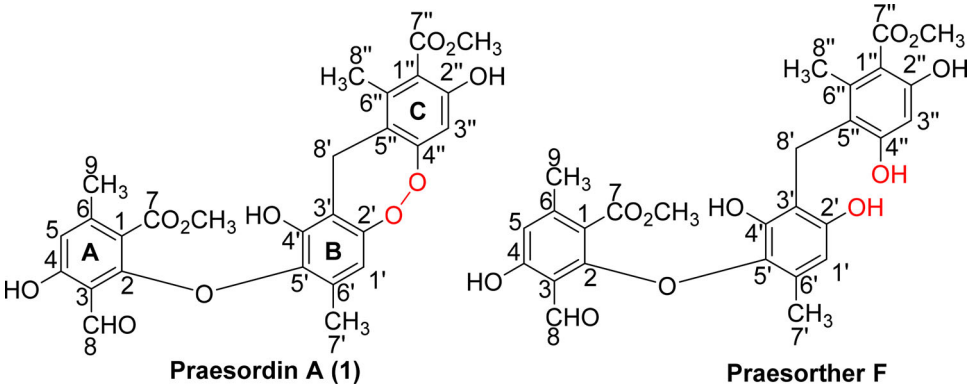

Figure 1. Chemical structures of compound **1** and praesorether F.

detected in this species at high concentrations [4–6]. As part of our continuing investigation of α-glucosidase inhibitors [7–9], this paper details the separation, structural characterization, and α-glucosidase inhibiton of one new diphenyl cyclic peroxide, named praesordin A (**1**), together with four depsidones, including virensic acid (**2**), protocetraric acid (**3**), 8′-*O*-methylprotocetraric acid (**4**) [10], and furfuric acid (**5**) [11] from *P. praesorediosum* collected in Dong Nai province, Vietnam (Figure 1).

2. Results and discussion

Compound **1** was isolated as a yellow solid. Its molecular formula was established as $C_{27}H_{24}O_{11}$ by HR-ESI-MS data (*m/z* 547.1212 $[M+Na]^+$; *m/z* 525.1396 $[M+H]^+$). IR absorptions detailed the presence of the hydroxyl (3394 cm^{-1}), carbonyl (1708 cm^{-1}), and olefin (1647 cm^{-1}) moieties. The ^{1}H-NMR spectrum of **1** (Table 1) exhibited one aldehyde proton at δ_H 10.44 (1H, *s*, H-8), three aromatic protons at δ_H 6.48 (1H, *dd*, 0.5 & 0.5 Hz, H-5), 6.18 (1H, *d*, 0.5 Hz, H-1′), 6.31 (1H, *s*, H-3″), two methoxy signals at δ_H 3.17 (3H, *s*, 7-OC$\underline{H}_3$) and 3.86 (3H, *s*, 7″-OC$\underline{H}_3$), two methylene protons at δ_H 3.97 (1H, *brs*, H-8′a) and 3.98 (1H, *brs*, H-8′b), and three methyl groups at δ_H 2.13 (3H, *d*, 0.5 Hz, H-9), 1.98 (3H, *s*, H-7′), 2.61 (3H, *s*, H-8″). The combination of ^{13}C-NMR and HSQC spectra of **1** (Table 1) revealed 27 carbons comprising one formyl carbon at δ_C 195.6 (C-8), two carbonyl carbons at δ_C 166.8 (C-7), 172.8 (C-7″), eighteen aromatic carbons in the range of 102.0-164.2 ppm (seven oxygenated and four methine carbons), two methoxy carbons at δ_C 52.0 (7-O$\underline{C}H_3$), 51.9 (7″-O$\underline{C}H_3$), one methylene carbon at δ_C 21.1 (C-8′), and three methyl carbons at δ_C 20.5 (C-9), 16.7 (C-7′), 19.5 (C-8″), which were proved the diphenyl ether skeleton owned three aromatic rings, in which rings A and B linked through an ether bridge, while rings B and C connected together via a methylene linkage at its C-3′ and C-5, similar to praesorether F [6]. However, the molecular formula $C_{27}H_{24}O_{11}$ of **1** affirmed sixteen degrees of unsaturation, supported by HR-ESI-MS data. Three aromatic rings, one formyl group, and two carbonyl moieties were accounted for fifteen degrees of unsaturation in **1** [6], and one existing degree of unsaturation was secured the present of the peroxide ring in **1**. On the other hands, the HMBC spectrum of **1** (Figure 2) signified correlations between two methylene protons at δ_H 3.97 (H-8′a),

Table 1. ^{1}H and ^{13}C NMR spectral data for compound **1** and praesorether F in acetone-d_6.

	1		Praesorether F	
Position	δ_H	δ_C	δ_H	δ_C
1		115.7		115.5
2		159.2		158.9
3		111.0		111.0
4		164.2		164.3
5	6.48 (*dd*, 0.5 & 0.5)	112.7	6.52 (*d*, 0.5)	112.9
6		148.1		148.2
7		166.8		166.6
8	10.44 (*s*)	195.6	10.44 (*s*)	195.6
9	2.13 (*d*, 0.5)	20.5	2.15 (*d*, 0.5)	20.5
1′	6.18 (*d*, 0.5)	108.5	6.24 (*s*)	108.9
2′		**153.9**		**153.3**
3′		113.7		113.1
4′		149.8		149.2
5′		135.7		135.8
6′		129.6		129.9
7′	1.98 (*s*)	16.7	1.99 (*s*)	16.6
8′	3.97 (*brs*)	21.1	3.97 (*brs*)	20.7
	3.98 (*brs*)		3.98 (*brs*)	
1″		107.1		109.4
2″		162.3		161.5
3″	6.31 (*s*)	102.0	6.33 (*s*)	101.5
4″		**163.5**		**160.0**
5″		120.8		119.5
6″		142.1		142.5
7″		172.8		172.4
8″	2.61	19.5	2.58	19.1
7-OCH_3	3.17	52.0	3.18	52.0
7″-OCH_3	3.86	51.9	3.88	52.1

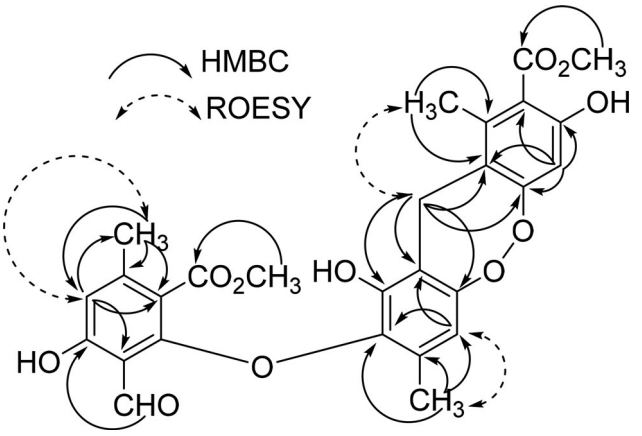

Figure 2. Key HMBC and ROESY correlations of **1**.

3.98 (H-8′b) and two oxygenated aromatic carbons at δ_C 153.9 (C-2′), 163.5 (C-4″), and furthermore, the observed downfield shifts of these carbons [at δ_C 153.9 (C-2′), 163.5 (C-4″) of **1**, and δ_C 153.3 (C-2′), 160.0 (C-4″) in praesorether F, in acetone-d_6] (Table 1), which were designated the 2′,4″-peroxo bridge. According to the above-mentioned analysis, the structure of **1** was established as shown, named praesordin A.

Table 2. α-Glucosidase inhibition of compounds **2–5**.

	Inhibition (%)					
Samples	250	100	50	25	10	IC_{50} (μM)
2	94.50 ± 1.10	46.79 ± 0.75	19.35 ± 0.69	2.40 ± 1.00	–	**110.1**
3	*	68.47 ± 0.95	23.90 ± 1.40	12.41 ± 0.84	6.70 ± 1.20	**79.3**
4	*	75.68 ± 0.88	51.94 ± 0.91	25.20 ± 1.80	4.70 ± 1.20	**48.2**
5	*	92.80 ± 1.30	56.90 ± 1.30	29.3 ± 1.10	10.30 ± 1.20	**43.7**
Acarbose						**214.5**

*Inhibition > 100%.
- Inhibition < 1%.

Compounds (**2**-**5**) were measured for their α-glucosidase inhibitory activity (Table 2). As results, compounds (**2**-**5**) expressed more potent inhibition against enzyme α-glucosidase (IC_{50} ranged from 43.7 to 110.1 μM) than the standard drug acarbose (IC_{50} = 214.5 μM).

Some natural cyclic peroxides were announced from others origins [12–14], however, this is the first time that diphenyl cyclic peroxide was enunciated from the lichen *Parmotrema praesorediosum*.

3. Experimental

3.1. General experimental procedures

The IR spectra were measured on Shimadzu FTIR-8200 infrared spectrophotometer. The HR-ESI-MS were recorded on a HR-ESI–MS MicroOTOF–Q mass spectrometer or on a LC-Agilent 1100 LC-MSD Trap spectrometer. NMR spectra were recorded on a Bruker Avance III spectrometer, using residual solvent signal as internal reference: acetone-d_6 δ_H 2.05, δ_C 206.31 and 30.6, at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. TLC was carried out on precoated silica gel 60 F_{254} or silica gel GF_{254} (Merck). Spots were visualized by spraying with 10% aqueous H_2SO_4 or 5% ferric chloride solutions followed by heating. Gravity column chromatography was performed with silica gel 60 (0.040–0.063 mm, Himedia).

3.2. Plant material

The lichen thalli of *Parmotrema praesorediosum* were collected on the bark of *Dipterocarpus* sp. at Tan Phu forest, Dong Nai province, Vietnam in June 2009. The geographical location where the lichen was collected is at an altitude of 110 m, 11°20′−11°50′ N and 107°09′−107°35′ E. The botanical species of *Parmotrema praesorediosum* (Nyl.) Hale (synonym of *Parmelia praesorediosa* Nyl.) was identified by Dr. Vo Thi Phi Giao, Faculty of Biology, University of Science, National University – Ho Chi Minh City. A voucher specimen (No US-B020) was deposited in the Herbarium of The Department of Organic Chemistry, Faculty of Chemistry, University of Science, National University – Ho Chi Minh City, Vietnam.

3.3. Extraction and isolation

The thallus material (5.0 kg) was washed under flow of tap water and then was air-dried at ambient temp. to obviate thermally induced decomposition prior to being ground into a fine powder. The ground powder sample (3.0 kg) was macerated by methanol at room temperature to afford a crude methanol extract (450 g). This crude one (450 g) was applied to silica gel solid phase extraction, successively eluted with the following solvents: petroleum ether (60 – 90 °C) (PE), chloroform (C), ethyl acetate (EA), acetone (A) and methanol (M) to afford corresponding extracts: extract PE (40 g), extract C (105 g), extract EA (50 g), extract A (45 g) and extract M (37 g).

The chloroform extract (105 g) was subjected to silica gel column chromatography, eluted by the solvent system of petroleum ether – ethyl acetate with increasing ethyl acetate to give twenty three fractions, coded C1 – C23. Fraction C16 (4.2 g) was rechromatographed, eluted with chloroform-methanol (95:5) to give **5** (15.0 mg). Fraction C19 (6.1 g) was applied on silica gel column and eluted with a gradient solvent system of chloroform-acetone (95:5) to give three fractions (C19a, C19b and C19c). Fraction C19b (3.2 g) was rechromatographed, eluted with chloroform-acetone (98:2) to give six fractions (C19ba to C19bf). Fraction C19ba (169.6 mg) was subjected to pre TLC (chloroform-methanol, 95:5, 9:1 and *n*-hexane-diethyl ether, 5:5) to afford compound **1** (10.5 mg).

The acetone extract (45.0 g) was applied to silica gel column chromatography and eluted with ethyl acetate–methanol (9:1-5:5) to give 6 fractions (from AC.1 to AC.6). Subfraction AC2 (2.5 g) was applied to column chromatography, eluting with chloroform–acetone–acetic acid (95:5:3 drops) to yield **2** (5.2 mg) and **4** (5.0 mg). Fraction AC5 (28 g) was rechromatographed, eluted with chloroform-acetone (7:3-5:5) to give **3** (2.0 g).

3.3.1. Praesordin A (1)

Yellow solid; IR (KBr) υ_{max}: 3394, 1708, 1647, 1272 cm^{-1}. ^{1}H-NMR (acetone-d_6, 500 MHz, *J* in Hz) and ^{13}C-NMR (acetone-d_6, 125 MHz) spectral data see Table 1; HR-ESI-MS: *m/z* 547.1212 $[M + Na]^+$ (calcd for $C_{27}H_{24}O_{11}Na$, 547.1216); 525.1396 $[M + H]^+$ (calcd for $C_{27}H_{25}O_{11}$, 525.1397).

3.4. α-Glucosidase inhibition assay

Compounds **2-5** were evaluated their inhibitory activity against enzyme α-glucosidase as previously described paper, and acarbose was used as the positive control [7–9].

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Disclosure statement

No potential conflict of interest was reported by the authors.

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