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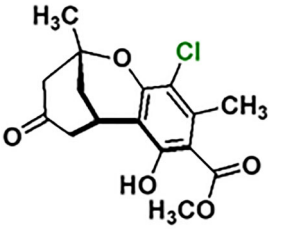
Dilatatone, a new chlorinated compound from *Parmotrema dilatatum*

Hoang-Vinh-Truong Phan[a], Asshaima Paramita Devi[b], Hoang-Duy Le[c], Thanh-Trung Nguyen[d], Huu-Hung Nguyen[e], Tran-Thai-Duong Le[f], Tai Hoang Nguyen[g], Jirapast Sichaem[h] and Thuc-Huy Duong[a]

[a]Faculty of Chemistry, University of Education, Ho Chi Minh City, Vietnam; [b]Center of Excellence in Natural Products Chemistry, Department of Chemistry Faculty of Science, Chulalongkorn University, Pathumwan, Bangkok, Thailand; [c]Department of Chemistry, Pham Van Dong University, Quang Ngai, Vietnam; [d]Institute of Research and Development, Duy Tan University, Da Nang, Vietnam; [e]Faculty of Environment and Biotechnology, Van Lang University, Ho Chi Minh City, Vietnam; [f]Institute of Drug Quality Control, Ho Chi Minh City, Vietnam; [g]Center of Research and Application Biology, Ho Chi Minh City, Vietnam; [h]Faculty of Science and Technology, Thammasat University, Lampang, Thailand

ABSTRACT

Chemical investigation of the lichen *Parmotrema dilatatum* led to the isolation of a new chlorinated compound, named dilatatone (**1**), along with a known compound, sernanderin (**2**). Their chemical structures were determined by analysis of their 1 D and 2 D NMR spectra, HRESIMS, and ECD data. Both compounds showed weak α-glucosidase inhibitor activity.



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1. Introduction

Chemists have been turning their attention to bioactive lichen metabolites, in particular phenolic compounds such as depsides, depsidones, and diphenyl ethers (Boustie and Grube 2005; Thadhani et al. 2011; Kellogg and Raja 2017). *Parmotrema* form a large genus in the family Parmeliaceae. Three of its members, *P. tsavoense*, *P. sanctiangelii*, and *P. praesorediosum,* are native to Vietnam (Duong et al. 2018a, 2018b).

CONTACT Jirapast Sichaem jirapast@tu.ac.th, huydt@hcmue.edu.vn

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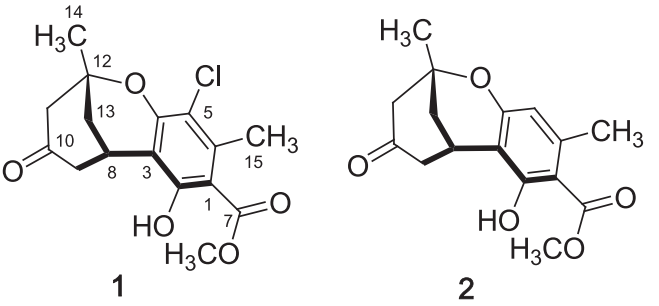

Figure 1. Chemical structures of **1** and **2**.

Investigation of these lichens has resulted in the isolation of many novel compounds with interesting biological properties. As part of our systematic research on bioactive Vietnamese lichens, we examined *Parmotrema dilatatum*, which is widely distributed at high altitudes in the south of Vietnam. Little is known about the chemistry of *P. dilatatum*, with a single published report having isolated two major components, salazinic acid and atranorin (Honda et al. 2010). In this paper, we report the isolation of a new compound, dilatatone (**1**), together with a known one, sernanderin (**2**) (Kinoshita et al. 2004) (Figure 1). Their chemical structures were elucidated by interpretation of spectroscopic data. All isolated compounds were also examined for their α-glucosidase inhibitory activity.

2. Results and discussion

Compound **1** was isolated as a white amorphous powder. The molecular formula was established to be $C_{16}H_{17}O_5Cl$ on the basis of the positive-ion mode HRESIMS data with a sodiated ion peak at m/z 347.0660 (calcd. for $C_{16}H_{17}O_5ClNa$ 347.06583). The ^{1}H NMR and HSQC spectra of **1** showed the presence of one hydrogen-bond hydroxyl group (δ_H 11.75, s), one sp^3 methine group (δ_H 3.66, m), three diastereotopic methylene groups (δ_H 2.70, m and 2.53, m; 2.65, m and 2.38, 16.0, m; 2.23, dd, $J = 13.6$, 2.4 Hz and 2.03, m), one methoxy group (δ_H 3.86, s), and singles for two methyl groups (δ_H 2.49 and 1.55). Supporting the HSQC analysis, the ^{13}C NMR spectrum suggested the presence of one ketone carbonyl carbon (δ_C 208.2), one ester carbonyl carbon (δ_C 172.1), three methylene groups (δ_C 53.3, 45.8, and 34.6), one methoxy group (δ_C 52.3), one methine carbon (δ_C 26.8) and two methyl groups (δ_C 28.6 and 19.7), and seven quaternary carbons, three of which were oxygenated (δ_C 159.2, 153.2, and 78.9). The downfield methine proton at δ_H 3.66 (H-8) gave HMBC cross peak to the carbon at δ_C 153.2 (C-4), indicating that this group attached at C-3. Three methylene moieties at δ_H 2.70/2.53 (H_2-9), 2.23/2.03 (H_2-13), and 11.75 (2-OH) showed HMBC correlations to the same carbon at δ_C 110.6 (C-3), suggesting direct linkages of H_2-9/H-8/H_2-13. The HMBC correlations of H_2-9 and H_2-11 (δ_H 2.65/2.38) to the carbon at δ_C 208.8, indicating the presence of the ketone carbonyl carbon at C-10. Both H_2-11 and H_3-14 (δ_H 1.55) showed HMBC cross peaks to C-13 and carbon at δ_C 78.9, defining the connectivity as arising through C-11-C-14 at C-12 (Figure S1). The ^{13}C chemical shift of C-12 (δ_C 78.9) indicated its oxygenated status. Taken together, the spectroscopic data suggested a

molecular formula of $C_{16}H_{17}O_5$ and 7 DBEs. The remaining DBE together with the molecular formula of **1** indicated ether linkage between C-12 and C-4. The NMR data of **1** were showed that they similar to those of sernanderin (**2**) (Kinoshita et al. 2004), differing only in the presence of a chlorine atom instead of the aromatic proton at C-5. Further HMBC correlations of H_3-15 to C-1 (δ_C 105.9), C-5 (δ_C 114.7), and C-6 (δ_C 138.2) confirmed this.

The null optical rotation of **1** and the absence of Cotton effects in the ECD spectrum indicated that **1** is racemic, which has been occurred in a natural racemic compound **2** (Kinoshita et al. 2004). Thus, compound **1** was identified as dilatatone, and is shown as Figure 1.

Lichen metabolites have demonstrated promising results as a reservoir of biological active compounds (Karunaratne et al. 2014). The review establishes that the lichen extracts, especially of *Parmotrema* sp. has shown promising potential in the α-glucosidase inhibitory assay (Thadhani and Karunaratne 2017). To the best of our knowledge, this is the first evaluation of the *in vitro* anti α-glucosidase activity of this type of compounds (**1** and **2**). Both compounds **1** and **2** showed weak α-glucosidase inhibitory activity with IC_{50} values of 181.8 ± 0.27 and 146.0 ± 0.06 μM, respective. This result suggests that the α-glucosidase inhibitors from *P. dilatatum* are other types of compounds (Thadhani and Karunaratne 2017).

3. Experimental

3.1. General experimental procedures

Spectroscopy was performed on a Bruker Advance III (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometer with TMS as internal standard recording NMR spectra. Chemical shifts are expressed in ppm with a reference of chlroform-*d* at δ_H 7.26 and δ_C 77.8. The HRESIMS were recorded on an HRESIMS Bruker micrOTOF Q-II. TLC was carried out on precoated silica gel 60 F_{254} or silica gel 60 RP–18 $F_{254}S$ (Merck Millipore, Billerica, Massachusetts, USA) and spots were visualised by spraying with 10% H_2SO_4 solution followed by heating. Gravity column chromatography was performed with silica gel 60 (0.040–0.063 mm) (HiMedia, Mumbai, India).

3.2. Lichen material

Lichen thalli were separated from rocks in Lam Dong province, Vietnam in August and September 2015. The scientific name was given by Dr. Wetchasart Polyiam, Lichen Research Unit, Department of Biology, Faculty of Science, Ramkhamhaeng University, Thailand. A voucher specimen (No. US-B033) was deposited at the Herbarium of the Department of Organic Chemistry, University of Science, National University, Ho Chi Minh City, Vietnam.

3.3. Extraction and isolation

The lichen thalli were air-dried and ground, and 703 g of the ground material was macerated in acetone (3×10 L) at room temperature. The solution was filtered and

concentrated *in vacuo* to afford a crude acetone extract (112.54 g). The acetone crude extract was subjected to normal phase silica gel quick column chromatography, and eluted consecutively with *n*-hexane, dichloromethane, ethyl acetate, acetone, and methanol to yield five fractions: **PH** (3.02 g), **PC** (6.17 g), **PEA** (44.53 g), **PA** (31.71 g), and **PM** (4.91 g), respectively. The **PH** fraction (3.02 g) was subjected to normal phase silica gel column chromatography (CC) and eluted with solvent system *n*-hexane:ethyl acetate (8.0:2.0) to obtain five fractions: **MT1** (1.57 g), **MT2** (0.37 g), **MT3** (0.32 g), **MT4** (0.19 g), and **MT5** (0.55 g). Fraction **MT3** was further subjected to normal phase CC and isocratically eluted with *n*-hexane:ethyl acetate:acetone:acetic acid (8.0:2.0:0.4:0.1, v/v/v/v) to yield three subfractions, denoted **MT3.1**-**3**. **MT3.3** was purified by reverse-phase CC using the mobile phase of methanol–water (3:1, v/v), yielding compounds **1** (2.6 mg) and **2** (4.3 mg).

3.3.1. Dilatatone (1)

White amorphous powder, $[\alpha]\ ^{25}_{D}$ 0 (*c* 0.01, $CHCl_3$); HRESIMS *m/z* 347.0660 (M + Na; calcd for $C_{16}H_{17}O_5ClNa$, 347.0658); ^{1}H NMR (400 MHz, acetone-d_6) δ_H 11.75 (1 H, s, 2-OH), 3.86 (3 H, s, H-16), 3.66 (1 H, m, H-8), 2.70 (1 H, m, H-9a), 2.53 (1 H, m, H-9b), 2.65 (1 H, m, H-11a), 2.38 (1 H, d, 16.0 Hz, H-11b), 2.49 (3 H, s, H-15), 2.23 (1 H, dd, 2.4 Hz, 13.6 Hz, H-13a), 2.03 (1 H, m, H-13b), 1.55 (3 H, s, H-14); ^{13}CNMR (100 MHz, acetone-d_6) δ_C 208.2 (C-10), 172.1 (C-7), 159.2 (C-2), 153.2 (C-4), 138.2 (C-6), 114.7 (C-5), 110.6 (C-3), 105.9 (C-1), 78.9 (C-12), 53.3 (C-11), 52.3 (C-16), 45.8 (C-9), 34.6 (C-13), 28.6 (C-14), 26.8 (C-8), 19.7 (C-15).

3.4. α-Glucosidase inhibitory activity

α-Glucosidase inhibitory activity against baker's yeast was applied from a previous procedure (Sichaem et al. 2017). Enzymatic activity was quantified by measuring absorbance at 405 nm (ALLSHENG micro plate reader AMR-100). Acarbose® was used as a positive control (IC_{50} 93.6 ± 0.49 μM). Each of the compounds was tested with three concentrations. The mean values and standard deviations were determined. IC_{50} values were calculated using Microsoft Excel software.

4. Conclusions

In this study, two secondary metabolites (**1** and **2**) were isolated from *P. dilatatum* and their structures were elucidated as dilatatone (**1**) and sernanderin (**2**). To the best of our knowledge, compound **1** is a new chlorinated compound having a unique skeleton that are rarely reported from natural products, whereas **2** was isolated from this lichen for the first time. Compounds **1** and **2** exhibited weak α-glucosidase inhibitory activity.

Disclosure statement

No potential conflict of interest was reported by the authors.

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ORCID

Jirapast Sichaem https://orcid.org/0000-0003-1407-496X
Thuc-Huy Duong http://orcid.org/0000-0001-9891-4326

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