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Indicuen, a new hopane from *Parmotrema indicum* Hale growing in Vietnam

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ABSTRACT

One new hopane-type triterpene, indicuen (**1**), along with eight known compounds (**2–9**) were isolated from the *n*-hexane extract of the lichen *Parmotrema indicum* Hale. The chemical structures of isolated compounds were identified by interpretation of their spectroscopic data (1D, 2D NMR and HRESIMS) combined with DFT-NMR chemical shift calculations and subsequent assignment of DP4+ probabilities and by comparison with the literature. Indicuen represents for a rare hopane bearing a 1-carboxyethyl substituent at C-21 in lichens. Compounds **1–3** and **5–8** were evaluated for α-glucosidase inhibition and cytotoxicity against K562 and HepG2 cancer cell lines. Compounds **1**, **5** and **7** exhibited moderate α-glucosidase inhibition with IC$_{50}$ values of 201.1, 156.3 and 187.4 μM, respectively. Compound **1** also showed weak cytotoxicity toward K562 cell line while others showed no activity.

Parmotrema indicum
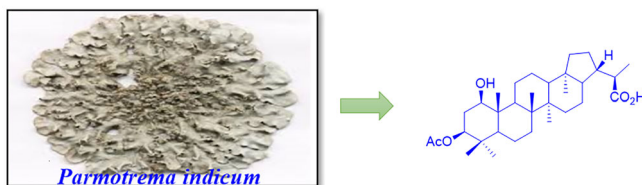
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1. Introduction

The genus *Parmotrema* has attracted attention from Vietnamese phytochemists. Diverse reports on chemical data of this genus indicated the presence of hundreds of bioactive compounds with a range of skeletal forms (Duong, Beniddir, et al. 2018; Duong, Ha, et al. 2018; Devi et al. 2020; Duong et al. 2020, 2021; Huynh et al. 2020; Do et al. 2021). However, fewer triterpenoids were reported from this genus. From the lichen *Parmotrema sancti-angelii*, six hopanes: hopane-6α,16α,22-triol, leucotylin, 16β-acetoxyhopane-6α,22-diol, 6α-acetoxyhopane-16β,22-diol, zeorin and 6α-acetoxyhopane-22-ol were isolated (Sichaem et al. 2019). Zeorin was found in *Parmotrema austrocetratum* (Ragasa et al. 2018). More recently, zeorin, leucotylin, lupeol, and betullinic acid were reported in *Parmotrema reticulatum* (Duong et al. 2021). Little is known about the lichen *Parmotrema indicum* Hale. A previous study on this lichen indicated the presence of a new compound, parmetherine D along with eight known phenolic compounds. In this article, the *n*-hexane extract of the lichen *Parmotrema indicum* was chemically investigated. A new hopane-type triterpene, indicuen (**1**), along with eight known compounds: 16β-acetoxyhopane-6α,22-diol (**2**) (Sichaem et al. 2019), 6α-acetoxyhopane-16β,22-diol (**3**) (Sichaem et al. 2019), zeorin (**4**) (König et al. 1999), hopane-3β,22-diol (**5**), betulinic acid (**6**) (Salimuzzaman et al. 1988), 3-oxobetulinic acid (**7**), betulin (**8**) (Tijjani et al. 2012) and ergosterol (**9**) (Nguyen et al. 2021) were isolated and elucidated (Figure 1). Compounds **1–3** and **5–8** were evaluated for α-glucosidase inhibition and cytotoxic activity against K562 and HepG2 cancer cell lines.

2. Results and discussion

Compound **1**, white amorphous powder, had a deprotonated ion peak at *m/z* 515.3749 on HRESI mass spectrum, determining the molecular formula $C_{32}H_{52}O_5$ (calcd. for $C_{32}H_{52}O_5$-H, 515.3736). The ^{1}H NMR and HSQC analysis exposed two oxymethine protons at δ_H 4.47 (1H, dd, $J = 12.0$, 4.5 Hz) and 3.55 (1H, dt, $J = 11.0$, 5.0 Hz), seven methyl groups (six singlets at δ_H 0.77, 0.85, 0.85, 0.93, 0.99, 1.02 and one doublet at δ_H 1.08, $J = 5.5$ Hz), one acetyl group at δ_H 1.99, six methines and nine methylenes. The JMOD, in accordance with HSQC spectrum, exhibited an acetyl group (δ_C 21.0 and 170.7), one carbonyl carbon (δ_C 178.6), two oxymethine carbons (δ_C 78.9 and 78.0), six methine carbons (δ_C 54.7, 53.6, 52.2, 50.0, 43.6 and 42.9), nine methylene carbons (δ_C
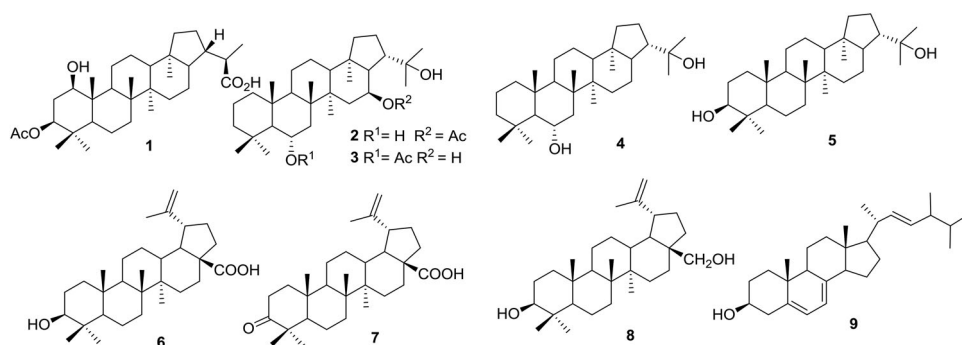

Figure 1. Chemical structures of **1–9**.

43.1, 41.8, 35.1, 34.3, 28.2, 24.7, 24.4, 20.7, and 18.7), seven methyl carbons (δ_C 28.2, 18.0, 17.3, 17.1, 16.6, 16.2 and 12.6), and five quaternary carbons (δ_C 45.1, 44.2, 42.8, 38.5 and 34.1). The presence of the acetyl group was determined by HMBC correlation of the methyl at δ_H 1.99 to carbonyl carbon at δ_C 170.7. These spectroscopic data suggested that **1** had a triterpene core with an additional acetyl group (Figure 1).

In the so-called A-ring, the COSY and HMBC correlations indicated structural elucidation. The HMBC correlations of both methyls at δ_H 0.85 (H$_3$-23 and H$_3$-24) to carbons at δ_C 78.0 (C-3), 38.5 (C-4) and 53.6 (C-5) and of proton at δ_H 4.47 (H-3) to C-4, C-5, and C-23 (δ_C 28.2), and the carbonyl carbon at δ_C 170.7 determined the position of the acetyl group at C-3. Likewise, the methyl at δ_H 0.93 (H$_3$-25) gave HMBC correlations to C-1 (δ_C 78.9), C-5 and C-10 defined the position of the hydroxy group at C-1. The COSY spectrum of **1** confirmed the spin system through H-1/H$_2$-2 and H$_2$-2/H-3 in the A-ring (Figure S1). The presence of the 1-OH group was defined by COSY correlation of 1-OH and H-1. The chemical features of the A-ring were similar to those of 1β-acetoxy-21α-hopane-3β,22-diol (Nguyen et al. 2021) or 3β-acetoxy-21α-hopane-1β,22-diol (Huneck et al. 1983).

HMBC and COSY correlations indicated the structures of the rings B-E. In particular, the HMBC correlations of the methyls at δ_H 0.93 (H$_3$-25) and 1.02 (H$_3$-26) to carbon at δ_C 52.2 (C-9), of both H$_3$-27 (δ_H 0.99) and H$_3$-26 to C-8 (δ_C 34.1) and C-14 (δ_C 42.8) and of H$_3$-27 and H$_3$-28 (δ_H 0.77) to C-13 determined the positions of the methyls H$_3$-25, H$_3$-27and H$_3$-28. COSY correlations through H-5/H-6/H-7, H-9/H-11/H-12/H-13, H-15/H-16/H-17/H-21 and H-19/H-20/H-21 finalized the structure of the rings B-E. All above spectroscopic data accounted for the C$_{32}$H$_{52}$O$_5$ moiety, leaving the remaining 1-carboxyethyl substituent at C-21. This finding was confirmed by HMBC correlations of H$_3$-29 to C-21, C-22 and C-30 and COSY correlations H$_3$-29/H-22/H-21.

The relative configuration of **1** was defined by NOESY correlations and *J*-coupling analysis. Analysis of the coupling pattern of H-3 (δ_H 4.47, 1H, dd, *J* = 12.0, 4.5 Hz) and H-1 (3.55 dt, *J* = 11.0, 5.0 Hz) indicated the two large *J* values, $J_{H-1/H-2a}$ = 12.0 Hz and $J_{H-3/H-2a}$ = 11.0 Hz. These values indicated that both protons H-3 and H-1 were oriented at α-orientation (axial position). This was confirmed by NOESY correlations of H-1/H-3 and H-3/H-5. Further, NOESY correlations of H$_3$-25/H$_3$-26, H$_3$-26/H-13, H-13/H-17 and H-17/H-21 indicated their same β-face. In contrast, the NOESY cross-peaks of H-5/H-9, H-9/H$_3$-27, H$_3$-27/H$_3$-28 and H$_3$-28/H$_3$-29 indicated that they were *syn*-facial. These spectroscopic data supported the 21α-hopane skeleton of **1**. However, the rapid rotation of the 1-carboxyethyl substituent led to the ambiguous assignment for the configuration of C-22. To the best of our knowledge, the presence of 1-carboxyethyl moiety at C-21 was very rare among lichen hopane-type triterpenoids. As a few examples, pyxinic acid and its ester from the lichen *Pyxine endochyrysina* possessed the 1-carboxy-1-hydroxyethyl group but their C-22 stereochemistry has not been assigned yet (Huneck and Yoshimura 1996). A literature review indicated that few 21-(1-carboxyethyl)-bearing hopanes have been reported in nature, resulting in some authors not defining C-22 configuration on such related scaffolds. Tuberosic acid is the first 21-(1-carboxyethyl)-bearing hopane isolated from the fern *Nephrolepsis tuberosa* (Dutta at al. 1993). Dutta and co-workers concluded the C-22 configuration as 22*S* but the evidence provided was insufficient to support the conclusion. Jaffe et al. (1987) synthesized two 22*R* and 22*S* isomers of 21α-hopane. However, these authors did not

provide any NMR data of each isomer. More recently, the C-22 configuration of fumi-hopaside A which had an additional hydroxy group at C-22 compared to **1** (Figure S2) was determined by single crystal X-ray crystallography (Ma et al. 2019). In our case, the unassigned C-22 configuration of **1** left two possible candidates of **1**, **1a** and **1b**. To determine the relative configuration of **1**, DFT-NMR calculations and DP4+ probability were undertaken. The plausible candidate **1b** was determined to have $22R^*$ configuration with 100% probability. Compound **1** was identified as indicuen, whose structure was shown in Figure 1.

A comprehensive review by Huneck and Yoshimura (1996) indicated the presence of over 30 10*R*-hopanes in lichens. The co-occurrence of hopanes **2**-**5** led to surmise that their biosynthesis might be related. From a biosynthetic perspective, compound **1** should share the same 10*R* configuration as **2**–**5**, thus, the absolute configurations of C-1, C-3 and C-22 were proposed as 1*R*, 3*S*, and 22*R*, respectively. Up to date, only six hopanes were reported in the genus *Parmotrema*, that is, *P. sancti-angelii*, *P. austroce-tratum* and *P. reticulatum* (Ragasa et al. 2018; Sichaem et al. 2019; Duong et al. 2021). Hopane-3β,22-diol (**5**) has been found for the first time in the genus *Parmotrema*. This compound was reported in the stem bark of *Abies veitchii* (Tanaka and Matsunaga 1992) but its complete NMR data has been not provided.

Compounds **1**–**3** and **5**–**8** were evaluated for α-glucosidase inhibition and cytotoxicity against K562 and HepG2. Compounds **1**, **5** and **7** exhibited moderate α-glucosidase inhibition with IC_{50} values of 201.1, 156.3 and 187.4 μM, respectively, compared with an acarbose positive control (IC_{50} 360 μM). Other compounds were inactive (Table S2). As regards cytotoxicity, only compound **1** showed moderate activity toward K562 cell line (IC_{50} 86.6 μM) while others failed to reveal any activity. The α-glucosidase inhibition by other isolates were reported (Duong et al. 2021; Mai et al. 2021) (Table S3).

3. Experimental

3.1. General experimental procedures

NMR spectra were recorded on a Bruker Avance III spectrometer (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) using residual solvent signals as internal references: acetone-d_6 at δ_H 2.05, δ_C 29.84 and chloroform-d at δ_H 7.26, δ_C 77.18. HRESIMS was recorded using an HRESIMS MicrOTOF–Q mass spectrometer on an LC-Agilent 1100 LC-MSD Trap spectrometer. Optical rotation was measured on a Jasco (Oklahoma City, OK, USA) P-1010 polarimeter. The IR spectra was measured on FT-IR/NIR SpectrometerFrontier/PerkinElmer, USA, instruments. UV spectra were obtained with a Perkin Elmer Lambda 25 UV–Vis spectrometer. Thin layer chromatography (TLC) was carried out on precoated silica gel 60 F_{254} or silica gel 60 RP–18 F_{254S} (Merck), and spots were visualized by spraying with 10% H_2SO_4 solution followed by heating. Gravity column chromatography was performed on silica gel 60 (0.040–0.063 mm, Himedia).

3.2. Lichen material

The thalli of the lichen *P. indicum* Hale were collected at Duc Trong District, Lam Dong Province, Vietnam in May 2020. The scientific name of the lichen was

determined by Dr. Thi-Phi-Giao Vo, Faculty of Biology, Ho Chi Minh University of Science, National University-Ho Chi Minh City. A voucher specimen (UEL-001) was deposited in the herbarium of the Department of Organic Chemistry, Ho Chi Minh University of Education.

3.3. Extraction and isolation

The clean, air-dried, and ground material (3.8 kg) was macerated with ethyl acetate extract at room temperature and the filtrated solution was concentrated under reduced pressure to afford the crude ethyl acetate extract (719.52 g). As the filtrated solution evaporated to dryness, a precipitate was collected (152.32 g). The crude extract was re-extracted using solvents of n-hexane and n-hexane: EtOAc extract (1/1, v/v), to afford an n-hexane extract (H, 112 g), n-hexane: ethyl acetate extract (HEA, 56 g) and the remaining (EAR, 70 g).

The extract H was washed with acetone to produce a precipitate (TH, 10 g) and solution (100 g). The precipitate TH was investigated in our previous study (Do et al. 2021). In this work, the solution part of extract H was undertaken. This part was applied to silica gel column chromatography (CC) and eluted with the gradient of n-hexane: EtOAc (20:1–1:1, v/v) to provide 8 fractions H1-H8. Fraction H2 (34 g) was dissolved in methanol and applied to Sephadex LH-20 gel chromatography, eluted with methanol to provide three fractions H2.1-3. Fraction H2.3 (7 g) was subjected to silica gel CC using the solvent system of n-hexane: CHCl$_3$: CH$_3$OH (20:10:1, v/v/v) as an eluent to afford three subfractions H2.3.1-2.3.3. Subfraction H2.3.3 (1.1 g) was applied to C$_{18}$ reverse-phase CC, eluted with CH$_3$OH: H$_2$O (20:1–10:1, v/v) to afford four fractions S1-S4. Fraction S3 (217 mg) was rechromatographed by C$_{18}$ reverse-phase CC, eluted with CH$_3$OH: H$_2$O (14:1, v/v) to afford three compounds **1** (4.2 mg), **2** (8.7 mg) and **3** (13.9 mg). Fraction S4 (95 mg) was applied to the same procedure to provide compound **5** (5.5 mg). Fraction H5 (4.5 g) was applied to silica gel CC, eluted with n-hexane: EtOAc: CHCl$_3$ (8:1:2, v/v/v) to afford three fractions H5.1-H5.3. Washing fraction H5.1 (800 mg) by acetone (100 mL × 5) gave a solid **9** (350 mg). Fraction H5.3 (1.5 g) was rechromatographed by silica gel CC, using the same solvent system as mentioned previously to provide four compounds **4** (87.6 mg), **6** (33.3 mg), **7** (12.3 mg) and **8** (21.5 mg).

3.3.1. Indicuen (1)

White amorphous powder. $[\alpha]_D^{25}$ +183 (c 0.1, MeOH). UV (MeOH) λ_{max} (logε) 225 (2.2) nm; IR cm^{-1} (neat): 3403, 1720, 1687, 1381, 1266. HRESIMS m/z 515.3749 [M − H]$^-$ (calcd for C$_{32}$H$_{51}$O$_5^-$, 515.3736); ^{1}H-NMR (500 MHz, acetone-d_6) and ^{13}C-NMR (125 MHz, acetone-d_6) See Tables S1 and S2.

3.4. α-Glucosidase inhibition assay

The α-glucosidase inhibition of **1–3** and **5–8** was determined using a method adapted from a previous method (Dao et al. 2021). All samples were analyzed in triplicate at five different concentrations around the IC$_{50}$ values, and the mean values were retained.

3.5. Cytotoxicity assay

The cytotoxicity of **1**-**3** and **5**-**8** was evaluated against the K562 and HepG2 cancer cell lines, followed our previous reports (Phan et al. 2020, Nguyen et al. 2020).

3.6. Computational details

DFT calculations were carried out using Gaussian 09 package (Frisch 2009). The conformational searching was done using xTB package. Then the stable conformers were estimated at the B3LYP/6-31 + G(d,p) level of theory. The frequency calculations were also taken at the same level to verify the structure of minimum energy on the potential energy surface. NMR calculations of conformers were performed at mPW1PW91/6-31 + G(d,p) by using Gauge-Independent Atomic Orbital (GIAO) methodology (Ditchfield 1974; Wolinski et al. 1990; Konstantinov and Broadbelt 2011). The modified DP4+ probability was utilized to assign the correctconformer of hopane using online implementation available from http://www-jmg.ch.cam.ac.uk/tools/nmr/DP4/ (Grimblat et al. 2015).

4. Conclusions

From the lichen *P. indicum*, nine compounds were isolated and elucidated, including indicuen (**1**), 16β-acetoxyhopane-6α,22-diol (**2**), 6α-acetoxyhopane-16β,22-diol (**3**), zeorin (**4**), hopane-3β,22-diol (**5**), betulinic acid (**6**), 3-oxobetulinic acid (**7**), betulin (**8**) and ergosterol (**9**). All isolated compounds in the title lichen have been reported for the first time. It was found that compound **1** is the first hopane bearing a 1-carboxyethyl group among lichen metabolites. Compounds **1**, **5** and **7** exhibited moderate α-glucosidase inhibition. Compound **1** also exhibited weak cytotoxicity toward K562 cell line.

Disclosure statement

No potential conflict of interest was reported by the authors.

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