Two new diketopiperazines and a new glucosyl sesterterpene from *Alternaria alternata*, an endophytic fungus from *Ceratostigma griffithii*

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\textbf{Abstract}

Two diketopiperazine derivatives, alternarizine A (1) and B (2), and a new glucosyl sesterterpene, 24-\(\alpha\)-\(\alpha\)-glucosyl-\((\rightarrow)\)-terpestacin (3), together with two known phytotoxic sesterterpenes, \((\rightarrow)\)-terpestacin (4) and fusaproliferin (5), were isolated from the fermentation broth of an endophytic fungus *Alternaria alternata*, which was obtained from the fresh root of *Ceratostigma griffithii*. Structures of all the isolates were identified by spectroscopic data.

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\textbf{1. Introduction}

*Alternaria* species belong to Deuteromycetes, have been identified as a prolific fungal source of secondary metabolites such as steroids, terpenoids, pyrones, quinones, phenolics and nitrogen-containing compounds, which exhibit a variety of biological activities (Lou et al., 2013). For instance, alternariosides and altenuenes, which were typical components from the genus *Alternaria*, were examined to have cytotoxicities (Aly et al., 2008) and antimicrobial (Jiao et al., 2006) properties. In the course of our ongoing research on the unique compounds from plant endophytes, *Alternaria alternata* as an endophytic fungus has been isolated and identified from *Ceratostigma griffithii*. The chemical investigation of its fermentation broth led to the isolation of two new diketopiperazine derivatives namely alternarizine A (1), altenarizine B (2) and a new glucosyl sesterterpene 24-\(\alpha\)-\(\alpha\)-glucosyl-\((\rightarrow)\)-terpestacin (3), along with two known phytotoxic sesterterpenes, \((\rightarrow)\)-terpestacin (4) and fusaproliferin (5). Details of the isolation, structure elucidation, and antibacterial activity of these compounds are discussed below.

It is well known that *Alternaria* sp. has the ability to produce various of terpenoids, including diterpenoids (Visconti et al., 1992), sesquiterpenoids (Gamboa-Angulo et al., 2002), triterpenoids (Gamboa-Angulo et al., 1997) and mixed terpenoids which have a multiple biogenesis (Ichihara et al., 1983; Kjer et al., 2009; Pero et al., 1973; Thomas, 1961). However, to the best of our knowledge, there are rare reports on sesterterpenoids from *Alternaria* sp. This phenomenon makes our group take the strain’s habitat into account. Qinghai-Tibet Plateau owns a special environment with high altitude, strong radiation, and large temperature difference between day and night. Thus, plants and endophytes which occupy this area should have special survival strategies including production of unique secondary metabolites (Fig. 1).

\textbf{2. Results and discussion}

Alternarizine A (1) was isolated as a yellow gum. Its molecular formula was assigned as C\(_{24}\)H\(_{28}\)N\(_2\)O\(_3\) on the basis of the HRESIMS ([M + H]\(^+\) at \(m/z\) 393.2171, calcd. for 393.2173). The IR spectrum showed the presence of two amide carbonyl signals at 1675 and 1670 cm\(^{-1}\); characteristic IR absorption bands indicated methylene (2934 cm\(^{-1}\)) and benzene (1634 cm\(^{-1}\)) groups. The \(^1\)H and \(^{13}\)C NMR spectra (Table 1) in combination with \(^1\)H→\(^1\)H COSY and HSQC recorded for 1 indicated the presence of a N-methylated phenylalanine (Phe) residue [\(\delta_H\) 7.40 (2H, t, \(J = 7.4\) Hz), 7.31 (1H, t, \(J = 7.4\) Hz), [E-mail address: zhouyan@cib.ac.cn (Y. Zhou).](mailto:zhouyan@cib.ac.cn)
The proton 1H, J = 7.4 Hz), 4.22 (1H, dd, J = 3.5, 4.5 Hz), 3.31 (1H, dd, J = 14.0, 3.5 Hz), 3.17 (1H, dd, J = 14.0, 4.5 Hz), 3.12 (3H, s); δC 165.8, 134.8, 130.6, 129.2, 127.9, 63.2, 36.7, 33.2]; a tyrosine (Tyr) unit [δH 6.7, 6.8 (4H, m), 5.5 (1H, br, s), 3.78 (1H, dd, J = 11.7, 2.9 Hz), 2.82 (1H, dd, J = 13.6, 2.9 Hz), 0.66 (1H, dd, J = 13.5, 11.7 Hz); δC 158.1, 130.3, 128.0, 115.3, 57.1, 39.8] and an isopentenyl group [δH 5.46 (1H, m), 4.44 (2H, d, J = 6.7 Hz), 1.79 (3H, s), 1.73 (3H, s); δC 138.2, 119.6, 64.8, 26.1, 18.1]. The HMBC cross peaks were observed between the N-methyl proton signal (δH 3.12) and the carbon signals of C-6 (δC 63.2) and C-2 (δC 165.8), which indicated the methyl group was at N-1. The correlations from the H-6 (δH 4.22) to C-5 (δC 165.6) and N-methyl (δC 33.2) and the correlation from the H-3 (δH 3.78) to C-2 (δC 165.8) confirmed the dikepiprezone core skeleton. The proton H-14 (δH 4.44) showed correlation peaks with the carbon signals of C-11 (δC 158.1) and C-10, 12 (δC 115.3), suggesting the connection of the isopentenyl group to C-11 via a oxygen atom. Thus, the primary structure of 1 was established as shown in Fig. 2. The relative stereochemistry of 1 was established by NOESY correlations of relevant protons as shown in Fig. 3. The presence of the NOE interaction between H-3 (δH 3.78) and H-6 (δH 4.22) indicated a boat form of the piperazine ring and the cis relationship between H-3 and H-6. The value of its negative optical rotation was close to those of (3S,6S)-3-benzyl-6-(4-hydroxybenzyl)-2,5-piperazinedione (Zeng et al., 2005), which suggested the 3S and 6S configuration of 1. A Marfey’s analysis had been done and the absolute configuration of

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**Table 1**

| Position | H (J in Hz) | C (J in Hz) |
|----------|-------------|-------------|
| 1        | –           | –           |
| 2        | 166.0       | –           |
| 3        | 3.83 d (11.6) | 96.9       |
| 4        | 5.71 s       | –           |
| 5        | –           | –           |
| 6        | 4.17 t (3.7)  | 63.5       |
| 7        | 2.90 dd (13.6, 2.9) | 39.7       |
| 8        | 0.85 dd (13.5, 11.6) | –         |
| 9, 13    | 128.0       | –           |
| 10, 12   | 128.0       | –           |
| 15       | 119.5       | –           |
| 16       | –           | –           |
| 17       | 1.73 s       | 26.0       |
| 18       | 1.73 s       | 26.0       |
| 19       | 3.22 dd (14.0, 3.5) | 35.8       |
| 20       | 3.11 dd (14.2, 4.5) | –         |
| 21, 25   | 134.8       | –           |
| 22, 24   | 130.7       | –           |
| 23, 23   | 115.3       | –           |
| N-Me     | 33.2        | –           |
| 23-OMe   | 33.2        | –           |

400 MHz for 1H and 100 MHz for 13C, in CDCl3.

Fig. 1. New compounds 1-3, and known compounds 4-5 isolated from Alternaria alternata.

Fig. 2. The 1H-1H COSY (bold lines) and key HMBC (H → C) correlations of 1.

Fig. 3. The key NOESY correlations of 1.
Therefore, the absolute configuration of 1 was established as (3S,6S)-3-benzyl-6-(4-isopropenylbenzyl)-2,5-piperazinedione, and it was named alternarizine A (1).

Alternarizine B (2) was obtained as a yellow gum, and its molecular formula was determined as C_26H_32NaO_7 by the HRESIMS ([M+Na]^+ at m/z 423.2283, calcld. 423.2278) with 12 degrees of unsaturation. IR absorptions implied the presence of aromatic ring (1300, 827 cm⁻¹) and amide carbonyl (1676, 1663 cm⁻¹). The NMR data was similar to alternarizine A (1), and the differences were the methoxyl instead of a proton at C-23 which created a group of typical para-substituted benzene signals [δ_H 6.92 (2H, d, J=8.5 Hz), 7.09 (2H, t, J=8.5 Hz); δ_C 114.5, 126.7, 130.7, 159.2] and an oxymethylene signal [δ_H 3.74 (3H,s); δ_C 55.4]. The final structure was established by 2D NMR experiments including HSQC and HMBC. The absolute configuration of 2 was established as 3S, 6S by the similarity of optical rotation of 1 and 2's.

24-α-α-Glucosyl-(−)-terestarpenic (3) was isolated as a yellow gum. The molecular formula C_{17}H_{20}O_{9} was confirmed by HRESIMS ([M+Na]^+ at m/z 587.3196, calcld. for 587.3191) and indicated 8 units of unsaturation. The IR spectrum showed absorption band at 3429 cm⁻¹, which suggested the presence of hydroxyl group in the molecule. Its 1H NMR spectrum (Table 2) exhibited signals due to three olefinic protons [δ_H 5.43 (1H, m), 5.34 (1H, m), 5.18 (1H, m)], a set of typical α-α-glucosyl signals [δ_H 4.78 (1H, d, 3.7), 3.58 (1H, m), 3.81 (1H, m), 3.37 (1H, m), 3.29 (1H, m), 3.67 (1H, m), 3.80 (1H, dd, 11.8, 2.3)], three vinyl methyl singlets [δ_H 1.67 (6H, s), 1.55 (3H, s), and two methyl singlets [δ_H 1.32 (3H, d, 7.0), 0.95 (3H, s)]. The 13C NMR spectrum (Table 2), displayed 31 carbon signals, and HMBC data indicated the presence of five CH$_2$ (including three vinyl methyl carbons at δ 10.6, 15.4, 15.5), eight CH$_2$ (including a α-α-glucosyl carbons at δ 6.27), eleven CH$_3$ (including three olefinic carbons at δ 123.5, 126.1, 130.1 and five α-α-glucosyl carbons at δ 71.9, 73.7, 74.2, 75.3, 100.5), and seven quaternary carbons (including five olefinic carbons at δ 133.9, 137.4, 138.7, 149.3, 151.8 and a keto carbon at δ 210.5). These data suggested that compound 3 is a bicyclic sesterterpenoid with a 2-hydroxyacryl ketone (three carbons at δ 151.8, 149.3, 210.5). 1H-1H COSY spectra suggested the presence of the spin systems —CH$_2$—CH—C(CH$_3$)$_2$—(A) [δ_H 5.34 (1H, m), 1.77 (1H, m), 2.34 (1H, m), 1.67 (3H, s); δ_C 138.7, 123.5, 40.4, 15.5], —CH$_2$—CH—C(CH$_3$)$_2$—B [δ_H 5.18 (1H, m), 2.31 (1H, m), 2.29 (1H, m), 2.10 (1H, m), 2.04 (1H, m), 1.67 (3H, s); δ_C 133.9, 126.1, 41.6, 25.0, 15.4], —CH$_2$—CH—CH(OH)—C [δ_H 3.99 (1H, m), 2.06 (1H, m), 1.77 (2H, m), 1.64 (1H, m); δ_C 77.1, 36.1, 30.9], (CH$_3$)$_2$—CH—CH$_2$—CH—CH$_3$—(D) [δ_H 5.43 (1H, m), 2.81 (1H, dd, 14.4, 7.0), 2.40 (1H, m), 1.90 (1H, m), 1.55 (3H, s); δ_C 137.4, 130.1, 50.4, 30.3, 10.6], —CH—CH$_2$—E [δ_H 3.89 (1H, dd, 9.5, 3.7), 3.73 (1H, dd, 9.5, 6.8), 2.84 (1H, m); δ_C 71.4, 36.3] and a set of typical α-glucosyl signals (F).

These were linked together with the help of HMBC data (Fig. 4). The correlations between H-5 (δ_H 2.29, 2.04) and C-4 (δ_C 138.7), between H-9 (δ_H 2.06, 1.77) and C-8 (δ_C 133.9), between H-11 (δ_H 3.99) and C-12 (δ_C 137.4), and between H-15 (δ_H 2.81) and C-1 (δ_C 50.2) linked and cyclized spin systems A, B, C, and D, in sequence. Both HMBC cross peaks between H-15 (δ_H 2.81) and C-16 (δ_C 151.8) and between H-19 (δ_H 0.95) and C-18 (δ_C 210.5) connected spin system D, A, and 2-hydroxyacryl ketone and created another 5-membered carboxylic ring system. Those correlations between H-23 and C-16 connected spin system E and 2-hydroxyacryl ketone and finally generated a terpentinyl-type sesterterpenoid. The HMBC correlation between the H-24 (δ_H 3.89, 3.73) and the terminal carbon (δ_C 100.5) confirmed the location of the glycosyl. The absence of the NOE interaction between H-15 (δ_H 2.81) and H-19 (δ_H 0.95) indicated that they were not in the same orientation. The sugar unit and aglycone component was determined to be α-glucopyranosyl and (−)-terestarpenic by TLC analysis of acid hydrolyzed 3 (Wu et al., 2015). Thus, the absolute configuration of 3 was deduced as 24-α-α-glucosyl-(−)-terstarpenic and was reinforced on the positive sign of the specific rotation [α]$_D^{20}$ = +38 for 3 and [α]$_D^{20}$ = −21.1 for −(−)-terstarpenic (Jin and Qiu, 2012).

Compounds 1–5 were tested against Candida albicans, Fusarium graminearum, Fusarium moniliforme, Saccharomyces cerevisiae, and Aspergillus niger. However, the compounds were inactive even at the high concentrations 100 μg/mL.

### 3. Experimental

#### 3.1. General

Optical rotations were determined on a Jasco P-1020 polarimeter at room temperature. UV spectra were recorded on a PerkinElmer Lambda 35 UV–vis spectrophotometer. IR spectra were measured by PerkinElmer one FT-IR spectrometer (KBr). 1D and 2D NMR were carried out on a Bruker-Ascend-400 MHz instrument at 300 K, with TMS as internal standard. HRESIMS was recorded on a Bruker Micro TOF-Q II mass spectrometer. Preparative HPLC was performed on a Waters 2545 equipped with a Kromasil RP-C18 column (10 × 250 mm, 5 μm) using a Waters 2489 UV detector. Column chromatography (CC) was performed with silica gel and Sephadex LH-20. All the solvent used were of analytical grade.

#### 3.2. Fungal material

The title strain was isolated from the root of C. griffithii, collected from the suburb of Lhasa, Tibet Autonomous Region, People's Republic of China. The culture was grown on potato dextrose agar (PDA) and distinguished morphologically as Alternaria sp., which was further reinforced by 18S rDNA sequence with a 99% identity to A. alternata. The strain (GenBank accession No. KR632488) has been preserved at Chengdu Institute of Biology, Chinese Academy of Sciences, China.

#### 3.3. Fungal culture and extraction

This fungus was cultivated on 4.8 L scale using 500 mL Erlenmeyer flasks containing 200 mL of the seed PDA medium for three days then on 60 L scale using 1 L Erlenmeyer flasks containing 10 mL seed PDA medium and 400 mL fermentation medium (soluble starch 0.8%, peptone 0.5%, NaCl 0.2%, CaCO$_3$ 0.2%,...
MgSO₄·7H₂O 0.05%, K₂HPO₄ 0.05%) for 14 days at 28 °C on a rotary shaker (250 rpm). The fermentation broth (60 L) of A. alternata was filtered. The filtrate was firstly extracted with petroleum and followed by EtOAc. The EtOAc solution was dried under vacuum and yielded 16 g extract.

3.4. Fractionation and isolation

The EtOAc residue (16 g) was separated into 4 fractions by CC on silica gel (300–400 mesh), eluting stepwise with CHCl₃/MeOH gradient (CHCl₃ 3CHCl₃/MeOH: 10:1 (v/v), CHCl₃/MeOH: 3:1 (v/v), MeOH). LC-MS analysis was performed on these fractions. The fourth fraction (eluted with MeOH) was sleeted. Sephadex LH-20 separation of this fraction (CHCl₃/MeOH: 1:1, v/v) afforded 3 subfractions (Fr.1–Fr.3). Fr.2 was further purified on a Waters preparative HPLC equipped with a Kromasil RP-C18 column (10 × 250 mm, ID × L; MeOH/H₂O: 70:30, v/v) to afford 1 (8.3 mg), 2 (2.5 mg), 3 (4.6 mg), 4 (10.3 mg), and 5 (4.7 mg).

3.4.1. Altenarizine A (1)

Yellow gum, [α]D²⁰ = −96 (c = 0.01, MeOH); IR (KBr) 2934, 1675, 1670, 1456, 1250, 1033, 827 cm⁻¹; UV (MeOH) λmax 227.3 (4.12), 276.3 (2.93); HRESIMS m/z [M + H]+ 393.2171 (calcd. 393.2173); ¹H NMR and ¹³C NMR are seen in Table 1.

3.4.2. Altenarizine B (2)

Yellow gum, [α]D²⁰ = −124 (c = 0.01, MeOH); IR (KBr) 2935, 1675, 1662, 1456, 1249, 1032, 825 cm⁻¹; UV (MeOH) λmax 226.9 (4.17), 275.7 (2.96); HRESIMS m/z [M + H]+ 423.2283 (calcd. 423.2278); ¹H NMR and ¹³C NMR are seen in Table 1.

3.4.3. 24α,α′-Glucosyl-(−)-terpestacin (3)

Yellow gum, [α]D²⁰ = +38 (c = 0.01, MeOH); IR (KBr) 3429, 2922, 1632, 1384, 1026, 557 cm⁻¹; UV (MeOH) λmax 262 (3.82); HRESIMS m/z [M + Na]+ 587.3196 (calcd. 587.3191); ¹H NMR and ¹³C NMR are seen in Table 2.

3.5. Absolute configuration of 1

An amino acid (N-methyl-l-phenylalnine or N-methyl-o-phenylalnine standard, 1 mg, Sigma, St. Louis, MO, USA) was dissolved in H₂O (30 µL) and treated with 1% 1-fluoro-2,4-dinitrophenyl-5-l-alanine amide (FDAA) in acetone (60 µL) and 6% Et₃N in 30 µL of H₂O at 40 °C for 1 h. After cooling to room temperature, the derivative was analyzed with UPLC with UV absorption of 340 nm. A HSS T3 column (50 mm × 2.1 mm i.d., 1.8 µm particles, Waters) was eluted with a linear gradient of 50–98% (v/v) CH₃OH–H₂O containing 0.1% TFA for 8 min. The standards gave the following retention times: 4.71 min for N-methyl-l-phenylalnine, and 5.95 min for N-methyl-o-phenylalnine. Compound 1 (1.1 mg) was hydrolyzed in 6N HCl (1 mL) and heated at 120 °C in a sealed vial for 12 h to yield the corresponding amino acids. The cooled reaction mixture was evaporated to dryness under reduced pressure, and HCl was removed from the residual acid hydrolysate by repeated evaporation from frozen H₂O (1 mL). The amino acid mixture was then treated in the same manner as the standards above (1% FDA and 6% Et₃N). The mixture of FDAA derivatives was filtered, and the filtrate was diluted with H₂O and analyzed by HPLC. The FDAA derivative of the amino acid liberated from 1 showed the peak at 4.71 min, matching the retention time of N-methyl-l-phenylalnine.

3.6. Acid hydrolysis

A solution of compound 3 (1.3 mg) in 2N aqueous HCl (5.0 mL) was refluxed at 80 °C for 2 h. The mixture was then diluted in water (10 mL) and extracted with EtOAc (3 × 3 mL). The combined water and EtOAc layers and evaporated to dryness to afford the glycoside and aglycone. The residue was analyzed by silica gel TLC by comparison with standard sugars and (−)-terpestacin. The solvent systems were n-BuOH–MeOH (4:1) for glycoside and CHCl₃–CH₂OH (10:1) for aglycone, and spots were visualized by spraying with H₃SO₄/EtOH (1:9), and then heated at 110 °C for 1 min. For the sugar of 3, the RF of glucose was 0.55, and the RF of aglycone was 0.62 by TLC, respectively.

3.7. Antimicrobial assay

The antibacterial activity was evaluated according to the reported procedure with little modification (Shaaban et al., 2012). Activity was determined using the Oxford cup method with medium (dextrose 20.0 g/L, beef infusion 10 g/L, NaCl 5 g/L, agar 17 g/L) respectively, inoculated with strains of Escherichia coli 1044 and Bacillus subtilis 1079. To each cup was added 200 µL of sample (compounds 1–5) dissolved in DMSO. Methylcellulose (5 µg/mL) and DMSO were used as positive and negative controls, respectively. The plates were incubated at 37 °C for 24 h. The antimicrobial activity was evaluated by measuring the diameter zone of growth inhibition against the test microorganism. MIC was detected complying with the method described by Kubo et al. (2004). All the test samples were dissolved in DMSO and the final concentration of DMSO was not over 5% (v/v). The final range of

![Fig. 4. The ¹H-¹H COSY (bold lines) and key HMBC (H → C) correlations of 3.](image-url)
test sample dilutions was between 50 and 0.19 μg/mL in the MHB broth. The final bacteria concentration in each dilution was 1 × 10^8 CFU/mL. The tubes were incubated at 37 °C for 24 h and then examined for evidence of the growth. MIC was determined as the lowest concentration of the antibacterial agents to inhibit bacterial growth. The antifungal activity was assayed by the Oxford cup method with medium [potato extract 20% (potato:water, w/v); boiling 20 min], dextrose 20.0 g/L, agar 17 g/L inoculated with strains of C. albicans, F. graminearum, F. vasinfectum, S. cerevisiae, and A. niger. The plates were incubated at 31 °C for 72 h.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phytol.2015.10.024.

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