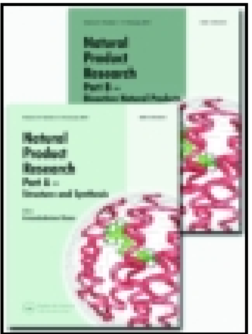

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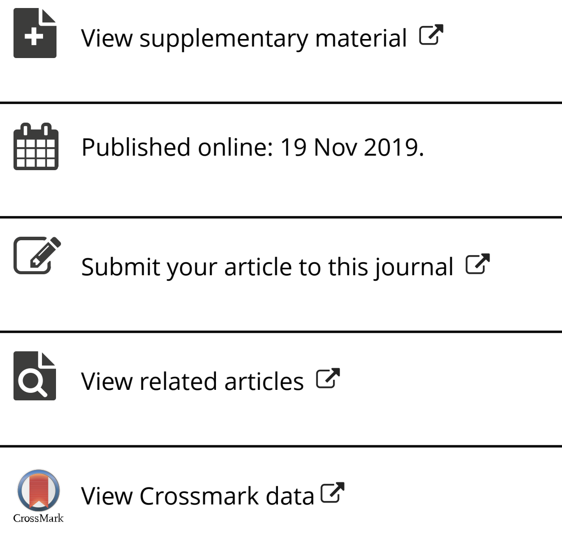

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Meroterpenoids and alkaloids from *Ganoderma australe*

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ABSTRACT

Two new mertoterpenoids, australins A (**1**) and B (**2**), and a new alkaloid, australine (**4**), together with five known compounds (**3**, **5**–**8**) were isolated from the fruiting bodies of *Ganoderma australe*. Their structures including absolute configurations were assigned by using spectroscopic methods and electronic circular dichroism (ECD) calculations. Racemic australin A was further purified by chiral HPLC. Biological assessments reveal that compounds (+)-**1** and **7** could significantly protect SH-SY5Y cells from glutamate-induced neural excitotoxicity.

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Ganoderma australe; meroterpenoids; alkaloids; neuroprotection

1. Introduction

Ganoderma fungal species have been found to have hypoglycemic (Seto et al. 2009), immunomodulatory (Hasnat et al. 2015), antitumor (Lu et al. 2004), and neuron protective properties (Cheung et al. 2000). Investigations on triterpenoids and

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polysaccharides in *Ganoderma* have lasted for decades (Isaka et al. 2018). Meroterpenoids in the genus *Ganoderma* didn't receive broad attention until our first isolation of linghziols, a pair of meroterpenoid enantiomers from *G. lucidum* (Yan et al. 2013). Thereafter, structurally diverse merotepenoids with intriguing biological activities were characterized from this genus (Luo et al. 2015; Zhou et al. 2015; Li et al. 2016; Luo et al. 2016; Wang et al. 2016; Liao et al. 2019; Luo et al. 2019). For the purpose of getting an insight into the chemical profile of meroterpenoids in *G. australe*, we have embarked an investigation on this fungal species which led to the isolation of meroterpenoids with neuroprotective activity (Zhang et al. 2019). During a follow-up study on this material, three meroterpenoids and five alkaloids were characterized. In this paper, we report their isolation, structure identification, and biological evaluation.

2. Results and discussion

Compound **1**, obtained as yellow gums, has the molecular formula $C_{15}H_{16}O_4$ based on analysis of its HRESIMS, ^{13}C NMR, and DEPT spectra, indicating 8 degrees of unsaturation. The ^1H NMR spectrum of **1** (Supplementary material, Table S1) exhibits a typical ABX spin system [δ_H 7.25 (1H, d, $J = 2.9$ Hz, H-3), 7.02 (1H, dd, $J = 8.9$, 2.9 Hz, H-5), 6.81 (1H, d, $J = 8.9$ Hz, H-6)]. The ^{13}C NMR and DEPT spectra (Supplementary material, Table S1) show 15 carbons including four sp^3 methylenes, four sp^2 methine, one sp^3 methine, and six quaternary carbons (including one carbonyl and one aldehyde group). The ^1H–^1H COSY spectrum (Supplementary material, Figure S2) of **1** shows correlations of H-2′/H-3′/H-4′ (δ_H 6.85), H-3′/H-8′, and H-6′/H-7′/H-8′ (Supplementary material, Figure S2, bold lines), in consideration of the HMBC correlations (Supplementary material, Figure S2) of H-6′, H-8′/C-4′ (δ_C 155.8) and H-7′/C-5′ (δ_C 142.9), indicate the presence of a hexatomic ring in **1** consisting of C-3′-C-8′. The observation of HMBC correlations of H-4′/C-9′ (δ_C 196.4), together with H-9′ (δ_H 9.39)/C-5′, C-6′ (δ_C 22.3), indicate that an aldehyde group is connected with C-5′. Further, C-2′ was deduced to be attached to C-2 *via* C-1′ based on the HMBC observations of H_2-2′ (δ_H 3.18, 3.20)/C-1′ (δ_C 205.8) and H-3/C-1′. Compound **1** was isolated as a racemic mixture. Further separation by chiral phase HPLC afforded (+)-**1** and (–)-**1**. To clarify the absolute configuration of each enantiomer, ECD calculation was used at B3LYP/6-31G(d,p) level. It was found that the calculated ECD spectrum matches well with the experiment one of (+)-**1** (Supplementary material, Figure S3). Their absolute configuration of were assigned to be 3′*R* for (+)-**1** and 3′*S* for (–)-**1**, respectively. Thus, the structure of **1**, named australin A, was finally identified.

Compound **2**, obtained as yellow solids, has the molecular formula $C_{15}H_{14}O_3$ (9 degrees of unsaturation) based on analysis of its HRESIMS, ^{13}C NMR, and DEPT spectra. The ^1H NMR spectrum of **2** (Supplementary material, Table S1) gives a typical ABX spin system [δ_H 7.34 (1H, d, $J = 2.9$ Hz, H-3), 7.00 (1H, dd, $J = 8.9$, 2.9 Hz, H-5), 6.79 (1H, d, $J = 8.9$ Hz, H-6)], a *meta*-disubstituted benzene ring [δ_H 7.19 (1H, t-like, $J = 7.6$ Hz, H-7′), 7.10 (1H, br s, H-4′), and 7.06 (2H, overlap, H-6′, H-8′)], and a methyl [δ_H 2.32, (3H, s, H_3-9′)]. The ^{13}C NMR and DEPT spectra (Supplementary material, Table S1) show 15 carbons including one methyl, one sp^3 methylene, seven sp^2 methines and six

quaternary carbons (including one carbonyl). These data resemble those of lingzhine C (Yan et al. 2015), the only difference is that C-9′ is a methyl in **2** instead of an aldehyde group in lingzhine C, which is consistent with the HMBC correlations (Supplementary material, Figure S2) of H_3-9′/C-4′, C-5′, C-6′. In addition, the observations of H_2-2′ (δ_H 4.24)/C-1′ (δ_C 205.6), C-3′, C-4′, C-8′, and H-3/C-1′ in the HMBC spectrum also allowed to confirm the structure of **2** as shown. As a result, the structure of **2**, named australin B, was deduced.

Compound **4** has the molecular formula $C_{14}H_{13}NO_4$ with 9 degrees of unsaturation deduced from its HRESIMS, ^{13}C NMR, and DEPT spectra. The ^{1}H NMR spectrum (Supplementary material, Table S1) shows three aromatic signals at δ_H 7.33 (1H, d, $J = 2.1$ Hz H-3), 6.82 (2H, overlap, H-5 and H-6). The ^{13}C NMR and DEPT spectra (Supplementary material, Table S1) display 14 carbons including one ethoxyl, six sp^2 methines and six quaternary carbons (including one carbonyl). These data are similar to those of lucidimine E (Lu et al. 2019). The only difference between them is that an ethoxyl in **4** instead of a methoxyl in lucidimine E is connected to C-7′ gaining supports from the HMBC correlation (Supplementary material, Figure S2) of H-8′ (δ_H 4.46)/ C-7′ (δ_C 166.1). This conclusion is also in accordance with the molecular formula $C_{14}H_{13}NO_4$ deduced from HR-ESI-MS. Thus, compound **4** was identified and named as australine. Of note, the presence of an methoxyl in lucidimine E and an ethoxyl in **4** prompted us to consider that they both might be an artifact produced during isolation procedures despite that LC-MS was not further conducted to secure our conclusion due to the minor nature of **4** and its analogs.

The known compounds were identified as lingzhine C (**3**) (Yan et al. 2015), ganocalicine B (**5**) (Huang et al. 2016), ganocochlearine C (**6**) (Wang et al. 2017), ganocochlearine A (**7**) (Tian et al. 2015), ganocochlearine H (**8**) (Wang et al. 2017), by comparison of their spectra data with the literature. Among them, compounds **6** and **8** were found to be racemates. An aliquote of **6** and **8** was respectively submitted to chiral HPLC to afford their enantiomers for biological test purpose.

In this study, all the compounds including the enantiomers of compounds **1**, **6**, and **8** were examined for their neuroprotective properties in glutamate-induced SH-SY5Y cells. The results show that (+)-**1** and **7** could significantly protect neural cells from excitotoxicity at 10 μM and almost reach the maximum effect at 20 μM (Supplementary material, Figure S4). The biological difference between **1** and **3** indicates that the absence of double bonds in the terpenoid part is advantageous for keeping the activity. Since excitotoxicity is implicated in multiple brain associated disorders such as stroke, anxiety, Alzheimer's disease (Mehta et al. 2013), the present findings suggest that meroterpenoids in the genus *Ganoderma* might be beneficial for neurodegenerative disorders.

3. Experimental

3.1. General experimental procedures

UV spectra were measured on a Shimadzu UV-2401PC spectrometer. Optical rotations were measured on a Bellingham + Stanley ADP 440 + digital polarimeter or a JASCO P-1020 digital polarimeter. CD were determined on a Chirascan instrument. NMR spectra

were recorded on a Bruker Avance 400 MHz or a Bruker Avance III 600 MHz or Bruker Avance 800 MHz spectrometer, with TMS (Tetramethyl silane) as an internal standard. ESIMS and HRESIMS were collected on an API QSTAR Pulsar 1 or an Agilent 6230 Q-TOF MS spectrometer. Column chromatography was undertaken on silica gel (200–300 mesh; Qingdao Marine Chemical Inc., Qingdao, China), C-18 silica gel (40–60 μm; Daiso Co., Japan), MCI gel CHP 20P (75–150 μm, Mitsubishi Chemical Industries, Tokyo, Japan) and Sephadex LH-20 (Amersham Pharmacia, Uppsala, Sweden) were employed for column chromatography. Semi-preparative HPLC was taken on a saipuruisi chromatograph with a YMC-Pack ODS-A column (250 × 10 mm, i.d., 5 μm), Preparative HPLC was taken on a Chuangxin-Tongheng chromatograph equipped with a Thermo Hypersil GOLD-C_{18} column (250 × 21.2 mm, i.d., 5 μm). Racemic compounds were purified by chiral HPLC on a Daicel Chiralpak column (IC, 250 mm × 10 mm, i.d., 5 μm) and a Daicel Chiralpak column (IC, 250 mm × 4.6 mm, i.d., 5 μm).

3.2. Fungal material

The fruiting bodies of *G. australe* were purchased from Traditional Chinese Medicine Market at Luosiwan International Trade City in Kunming, Yunnan province, PR China, in December 2014. The material was authenticated by Prof. Zhu-Liang Yang at Kunming Institute of Botany, Chinese Academy of Sciences, PR China, and a voucher specimen (CHYX-0588) is deposited at School of Pharmaceutical Sciences, Shenzhen University Health Science Center, PR China.

3.3. Extraction and isolation

The powdered fruiting bodies of *G. australe* (90 kg) were soaked with 95% EtOH (3 × 360 L × 24 h) to obtain a crude extract, which was suspended in H_2O followed by extraction with EtOAc for four times to afford an EtOAc-soluble portion (2.3 kg). This portion was submitted to a MCI gel CHP 20P column (MeOH/H_2O, 30%−100%) to provide seven parts (Fr.1 − Fr.7).

Fr.4 (367.0 g) was gel filtrated over Sephadex LH-20 (MeOH) followed by silica gel chromatography with increasing acetone in petroleum ether (2:1 − 1:1) to afford Fr.4.1 − Fr.4.4. Fr.4.3 (7.5 g) was divided into four parts (Fr.4.3.1 − Fr.4.3.4) by a RP-18 column (MeOH/H_2O, 55%−65%). Among them, Fr.4.3.1 (2.0 g) was gel filtrated over Sephadex LH-20 (MeOH) to afford Fr.4.3.1.1 and Fr.4.3.1.2. Fr.4.3.1.2 (300.0 mg) was separated by semi-preparative HPLC [MeOH/H_2O (0.05% TFA), 62%, flow rate: 2.5 mL/min] to afford compound **7** (5.8 mg, t_R = 7.8 min).

Fr.6 (124.7 g) was fractionated into five parts (Fr.6.1 − Fr.6.5) by a RP-18 column (MeOH/H_2O, 65%−90%). Fr.6.3 (16.2 g) was gel filtrated over Sephadex LH-20 (MeOH) to obtain Fr.6.3.1 and Fr.6.3.2. The later part (700.0 mg) was cut into nine parts (Fr.6.3.2.1 − Fr.6.3.2.9) by preparative HPLC (MeOH/H_2O, 40%−65%). Among them, Fr.6.3.2.5 (87.0 mg) was separated by semi-preparative HPLC (aqueous AcCN with 0.05% TFA in water, 26%, flow rate: 3 mL/min) to get compounds **5** (8.0 mg, t_R = 14.0 min), **8** (1.2 mg, t_R = 15.3 min), **6** (0.8 mg, t_R = 17.7 min), and Fr.6.3.2.5.1. Fr.6.3.2.5.1 (17.0 mg) was fractionated by semi-preparative HPLC [MeOH/H_2O (0.05%

TFA), 50%, flow rate: 3 mL/min] to obtain compound **3** (2.5 mg, t_R = 27.7 min). Fr.6.3.2.7 (50.0 mg) was fractionated by semi-preparative HPLC [aqueous AcCN (0.05% TFA), 42%, flow rate: 3 mL/min] to obtain compound **4** (3.1 mg, t_R = 22.8 min). Similarly, Fr.6.3.2.8 (68.0 mg) was separated by semi-preparative HPLC (aqueous AcCN with 0.05% TFA in water, 42%, flow rate: 3 mL/min) to get compound **1** (1.4 mg, t_R = 23.0 min). Fr.6.4 (35.0 g) was gel filtrated over Sephadex LH-20 (MeOH) to obtain Fr.6.4.1-Fr.6.4.3. Fr.6.4.3 (2.5 g) was divided into Fr.6.4.3.1 and Fr.6.4.3.2 by a MCI gel CHP 20P column (MeOH/H_2O, 60%−100%). Fr.6.4.3.1 (1.8 g) was submitted to vacuum liquid chromatography with increasing mixtures of ethyl acetate and ethanol (1:1) in petroleum ether (500:1 − 5:1) to afford eight sections (Fr.6.4.3.1.1 − Fr.6.4.3.1.8). Among them, Fr.6.4.3.1.3 (216.0 mg) was separated by preparative HPLC (MeOH/H_2O, 55%-100%) to obtain Fr.6.4.3.1.3.1 − Fr.6.4.3.1.3.6. Of them, Fr.6.4.3.1.3.4 (15.0 mg) was segregated by semi-preparative HPLC [MeOH/H_2O (0.05% TFA), 55%, flow rate: 3 mL/min] to acquire compound **2** (3.1 mg, t_R = 22.5 min).

New compound **1** is racemic, which was further purified by chiral phase on Daicel Chiralpak IC (flow rate: 3 mL/min) to afford enantiomers (+)-**1** (0.5 mg, t_R = 9.9 min) and (–)-**1** (0.7 mg, t_R = 11.8 min) (*n*-hexane/ethanol containing 0.05% TFA, 85:15).

3.4. Spectral data

3.4.1. Australin A (1)

Yellow gums; UV (MeOH) λ_{max} (logε) 370 (3.37), 231 (4.10) nm; {$[\alpha]_D^{25}$ −66.7 (*c* 0.13, MeOH); CD (MeOH) $\Delta\varepsilon_{222}$ −1.50, $\Delta\varepsilon_{235}$ −0.55, $\Delta\varepsilon_{245}$ −0.99, $\Delta\varepsilon_{325}$ +0.32, $\Delta\varepsilon_{376}$ −0.14; (−)-**1**}; {$[\alpha]_D^{25}$+102.6 (*c* 0.13, MeOH); CD (MeOH) $\Delta\varepsilon_{224}$ +1.00, $\Delta\varepsilon_{236}$ +0.62, $\Delta\varepsilon_{243}$ +0.75, $\Delta\varepsilon_{320}$ −0.21, $\Delta\varepsilon_{372}$ +0.05; (+)-**1**}; ESIMS *m/z* 259 $[M-H]^-$; HRESIMS *m/z* 259.0977 $[M-H]^-$ (calcd for $C_{15}H_{15}O_4$, 259.0976); ^1H and ^{13}C NMR data see Table S1 (Supplementary material).

3.4.2. Australin B (2)

Yellow solids; UV (MeOH) λ_{max} (logε) 366 (4.31), 257 (4.59), 211 (5.04) nm; ESIMS *m/z* 241 $[M-H]^-$; HRESIMS *m/z* 241.0870 $[M-H]^-$ (calcd for $C_{15}H_{13}O_3$, 241.0870); ^1H and ^{13}C NMR data see Table S1 (Supplementary material).

3.4.3. Australine (4)

Yellow solids; UV (MeOH) λ_{max} (logε) 354 (4.45), 287 (4.54), 261 (4.74), 206 (5.07) nm; ESIMS *m/z* 260 $[M+H]^+$; HRESIMS *m/z* 260.0919 $[M+H]^+$ (calcd for $C_{14}H_{14}NO_4$, 260.0917); ^1H and ^{13}C NMR data see Table S1 (Supplementary material).

3.5. Biological assay

A human neuroblastoma cell line (SH-SY5Y) was purchased from Cellcook Company in Guangzhou, PR China. The experimental procedures of cell culture and treatments were performed as described previously (Zhang et al. 2019). Briefly, cells were cultured in Dulbecco's modified Eagle's medium (DMEM, Gibco, Grand Island, NY, USA) with the addition of 10% fetal bovine serum (FBS, Gibco, Australia), 100 U/mL penicillin and

100 U/mL streptomycin (HyClone, Australia) at 37 °C and plated at a density of 4×10^4/well of a 96-well plate for 24 h. Thereafter, cells were pretreated with compounds (10, 20 and 40 μM) or phosphate buffer solution (PBS, HyClone, Utah, USA) for 24 h followed by a 24-h stimulation of either 10 mM glutamate (sigma) or PBS. After all treatments, 10 μL/well of CCK-8 solution was added into each well and incubated for 1 h. The absorbance was determined at 450 nm by using a microplate reader (BioTek).

All biological data are presented as means ± standard error of the mean (SEM) of the indicated 6 independent experiments. Statistical analyses were performed by One-Way ANOVA following by a post-hoc multiple-comparison Tukey test. $^{*}p < 0.05$ ($^{**}p < 0.01$, $^{***}p < 0.001$) was considered to be significant.

4. Conclusion

Three mertoterpenoids and five alkaloids were isolated from the fruiting bodies of *G. australe*. Among them, new mertoterpenoid (+)-**1** and alkaloid **7** exhibit significant neuroprotective properties against glutamate-induced excitotoxicity in SH-SY5Y cells. The present study not only adds a new facet for chemical composition of *Ganoderma* fungi but also discloses the biological significance of meroterpenoids in this genus.

Disclosure statement

No potential conflict of interest was reported by the authors.

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