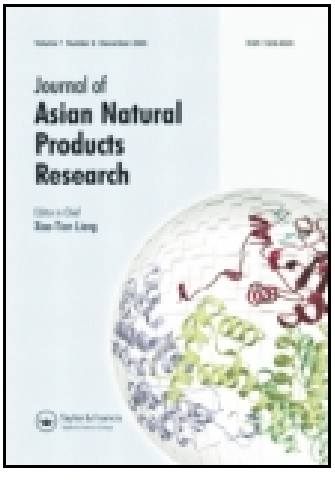

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New *Lycopodium* alkaloids from *Phlegmariurus squarrosus*

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Four new *Lycopodium* alkaloids (**1**–**4**), together with 15 known ones, were isolated from club moss *Phlegmariurus squarrosus*. Notably, 8α-hydroxylycojapodine A (**1**) was the first derivative of lycojapodine A (**5**) which was a novel C_{16}N-type *Lycopodium* alkaloid with an unprecedented 6/6/6/7 tetracyclic ring system. Their structures were elucidated based on the spectroscopic data, including 1D and 2D NMR techniques.

Keywords: *Phlegmariurus squarrosus*; *Lycopodium* alkaloids; 8α-hydroxylycojapodine A; 8β-acetoxy-12β-hydroxy-epidihydrolycopodine; 8β-acetyllycoposerramine-U; 11β-acetoxyl-*N*-methylhuperzine B

1. Introduction

The *Lycopodium* alkaloids, obtained from the club moss belonging to Lycopodiaceae, represent a large family of structurally diverse natural compounds often possessing unusual skeletons [1–3]. Most of them have attracted great interest from biogenetic, synthetic, and biological perspectives [1–6]. In our continuing efforts to search for structurally interesting and bioactive *Lycopodium* alkaloids, four new *Lycopodium* alkaloids, 8α-hydroxylycojapodine A (**1**), 8β-acetoxy-12β-hydroxy-epidihydrolycopodine (**2**), 8β-acetyllycoposerramine-U (**3**), and 11β-acetoxyl-*N*-methylhuperzine B (**4**) (Figure 1), together with 15 known ones, lycojapodine A (**5**) [7], lycodoline (**6**) [8], lycoflexine (**7**) [9], lycoposerramine U (**8**) [9], acetyllycopserramine U (**9**) [10], fawcettimine (**10**) [11], alopecuridine (**11**) [12], 8-β-acetoxyfawcettimine (**12**) [10], fawcettidine (**13**) [13], phlegmariurine B (**14**) [14], 8-deoxy-13-dehydroserratinine (**15**) [15], huperzine A (**16**) [16], huperzinine (**17**) [17], lycodine (**18**) [18], and des-*N*-methyl-β-obscurine (**19**) [18], were isolated from the club moss *Phlegmariurus squarrosus*. Herein, we describe the isolation and structure elucidation of **1**–**4**.

2. Results and discussion

The dried whole plants of *P. squarrosus* (7 kg) collected in Guangxi Province of China were extracted with 70% EtOH/H_2O three times at room temperature. The alkaloid fraction, obtained by acid–base extraction, was separated as described in Section 3 and yielded 19 alkaloids, including four new ones (**1**–**4**).

Compound **1** ($[\alpha]_D^{12.6}$ −49.2) was obtained as a colorless amorphous powder and its molecular formula was established as $C_{16}H_{23}NO_4$ by HR-EI-MS at *m*/*z* 293.1618 $[M]^+$, indicating six degrees of unsaturation. The IR absorptions at 3441, 1738, and 1686 cm^{-1} implied the presence of hydroxyl and carbonyl groups. Analysis

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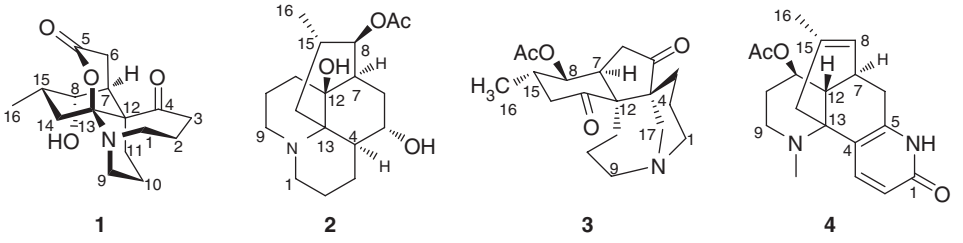

Figure 1. Structures of compounds **1**–**4**.

of the 1D and 2D NMR spectra revealed the existence of 16 carbons due to four quaternary carbons, three tertiary carbons, eight methylenes, and one methyl group (Table 1), which suggested **1** should be a *Lycopodium* alkaloid. Among them, one sp^3 quaternary carbon (δ_C 95.4) was ascribed to the carbon (C-13) bearing both an oxygen atom and a nitrogen atom, and two sp^2 quaternary carbons were attributable to the ketone group (δ_C 218.1) and the lactone group (δ_C 172.2). The $^1H-^1H$ COSY spectrum gave three fragments: **a** ($CH_2CH_2CH_2$), **b** (CH_2CH_2-CH_2), and **c** [$CH_2CHCHCH(CH_3)CH_2$] as shown in Figure 2. Further 2D NMR analysis indicated that compound **1** was similar to lycojapodine A, a known *Lycopodium* alkaloid first isolated from *L. japonicum* [7]. The only difference was that **1** had one more hydroxy group compared with that of lycojapodine A, which was connected to C-8 as deduced from the HMBC correlations for H-6a at δ_H 2.45–2.47, H-14b at δ_H 1.52, and H-16 at δ_H 1.03 to C-8 at δ_C 74.9. The ROESY spectrum of **1** showed cross-peaks of H-7/H-11b and H-15/H-6b that indicated H-7 was α-oriented and H-15 was β-oriented. H-8 was determined to be β-oriented based on the coupling constant between H-8 and H-7, and H-8 and H-15 [dd, 2.8 ($^3J_{H8-H7}$), 2.8 ($^3J_{H8-H15}$)] (Figure 2) [19]. Thus, the structure of compound **1** was elucidated as 8α-hydroxylycojapodine A.

Compound **2** ($[\alpha]_D^{20.2}$ + 8.61), a colorless amorphous powder, had a molecular formula of $C_{18}H_{29}NO_4$ as established by HR-EI-MS at *m/z* 323.2088 $[M]^+$, indicating five degrees of unsaturation. Analysis of the ^1H and ^{13}C NMR spectra of **2** (Table 1) revealed 18 carbon signals due to three quaternary carbons, five tertiary carbons, eight methylenes, and two methyl groups. The ^1H and ^{13}C NMR spectra of **2** were quite similar to those of 8β-acetoxy-12β-hydroxylycopodine [20,21]. The only difference was that **2** had one additional hydroxyl group instead of a ketone function. The hydroxyl group was attached to C-5 as inferred from the HMBC correlations from of H-5 at δ_H 3.99–4.01

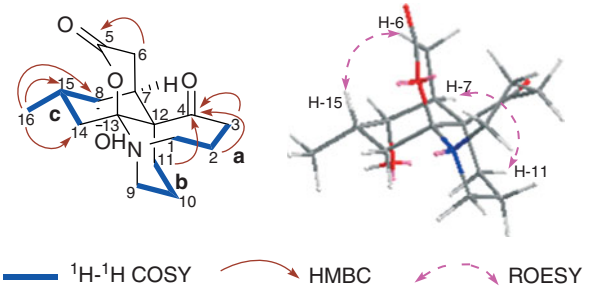

Figure 2. Selected 2D NMR correlations for **1**.

Table 1. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) data of **1**–**4** (δ in ppm, J in Hz).

	1[a]		**2**[a]		**3**[b]		**4**[a]	
No.	^{13}C	^{1}H (J in Hz)	^{13}C	^{1}H (J in Hz)	^{13}C	^{1}H (J in Hz)	^{13}C	^{1}H (J in Hz)
1a	51.9 t	3.76 (1H, td, 14, 3.2)	48.5 t	3.52 (1H, td, 13.2, 3.6)	52.2 t	3.32–2.34 (1H, m)	165.9 s	
1b		2.94–2.96 (1H, m)		2.86 (1H, dd, 13.2, 3.6)		3.18 (1H, d, 13.0)		
2a	27.5 t	2.09–2.11 (1H, m)	19.3 t	2.07–2.08 (1H, m)	17.4 t	2.16–2.18 (1H, m)	118.7 d	6.43 (1H, d, 9.3)
2b		1.71–1.73 (1H, m)		1.78 (1H, overlapped)		1.94 (1H, overlapped)		
3a	47.5 t	2.67–2.69 (1H, m)	22.2 t	2.04–2.05 (1H, m)	26.4 t	2.31–2.33 (1H, m)	142.9 d	7.95 (1H, d, 9.3)
3b		2.58–2.60 (1H, m)		1.62–1.64 (1H, m)		1.94 (1H, overlapped)		
4	218.1 s		36.5 d	2.71–2.73 (1H, m)	54.8 s		122.1 s	
5	172.2 s		66.0 d	3.99–4.01 (1H, m)	211.9 s		144.4 s	
6a	35.4 t	2.45–2.47 (1H, m)	29.9 t	1.96–1.98 (2H, m)	36.3 t	2.51–2.53 (1H, m)	30.3 t	2.96 (1H, dd, 18.0, 5.1)
6b		2.38 (1H, overlapped)				2.40–2.43 (1H, m)		2.32 (1H, d, 18.0)
7	44.1 d	2.38 (1H, overlapped)	45.1 d	2.12–2.14 (1H, m)	42.5 d	2.94–2.96 (1H, m)	31.2 d	2.71–2.73 (1H, m)
8	74.9 d	3.60 (1H, t, 2.8)	78.0 d	5.23 (1H, dd, 10.5, 5.5)	72.8 d	5.11 (1H, dd, 10.5, 4.5)	125.2 d	5.51 (1H, s)
9a	50.2 t	3.39–3.41 (1H, m)	47.3 t	3.81 (1H, td, 12.6, 3.6)	55.4 t	3.72–2.74 (1H, m)	49.7 t	2.74 (1H, overlapped)
9b		3.07–3.09 (1H, m)		2.94 (1H, dd, 12.6, 3.6)		3.06–3.08 (1H, m)		2.67–2.68 (1H, m)
10a	25.2 t	1.43–1.45 (1H, m)	19.4 t	2.34–2.36 (1H, m)	21.3 t	2.19–2.21 (1H, m)	26.4 t	1.87–1.89 (1H, m)
10b		1.39–1.41 (1H, m)		1.78 (1H, overlapped)		2.12 (1H, overlapped)		1.60–1.61 (1H, m)
11a	33.2 t	2.88 (1H, dd, 13.8, 6.1)	29.1 t	2.30–2.32 (1H, m)	34.4 t	2.34–2.16 (2H, m)	72.4 d	4.82 (td, 11.0, 5.3)
11b		2.08–2.09 (1H, m)		1.42–1.44 (1H, m)				
12	56.4 s		72.4 s		60.5 s		38.5 d	2.15 (1H, dd, 10.8, 3.3)
13	95.4 s		65.6 s		209.7 s		59.6 s	
14a	38.5 t	2.56–2.58 (1H, m)	33.6 t	2.44 (1H, dd, 12.7, 7.0)	44.7 t	2.50–2.54 (2H, m)	44.3 t	2.72–2.75 (1H, m)
14b		1.52 (1H, dd, 14.1, 4.9)		1.69 (1H, t, 12.7)				1.84 (1H, d, 16.6)
15	30.4 d	1.78–1.80 (1H, m)	28.8 d	3.29–3.31 (1H, m)	31.8 d	2.37–2.39 (1H, m)	134.2 s	
16	16.8 q	1.03 (3H, d, 6.7)	19.9 q	0.99 (3H, d, 6.7)	18.6 q	1.09 (3H, d, 6.4)	23.3 q	1.62 (3H, s)
17a					50.0 t	3.35 (1H, m)		
17b						2.90 (1H, dd, 14.6, 3.2)		
$CO\underline{C}H_3$			21.1 q	2.09 (3H, s)	21.0 t	2.13 (3H, overlapped)	21.2 q	2.09 (3H, s)
$CO\overline{CH}_3$			172.9 s		170.5 s		172.8 s	
$\overline{N}$-CH_3							37.7 q	2.70 (3H, s)

[a] Recorded in CD_3OD.
[b] Recorded in $CDCl_3$.

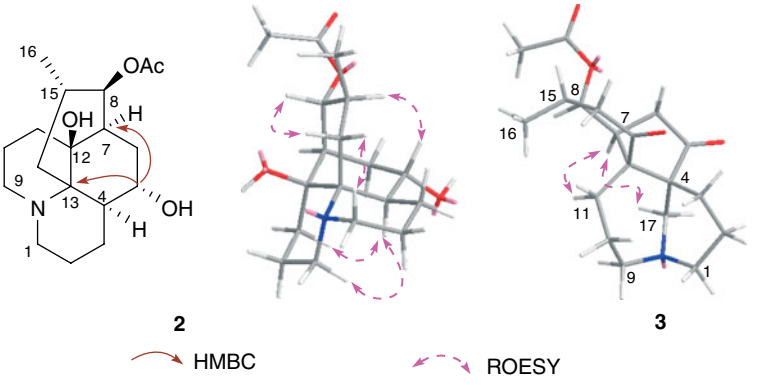

Figure 3. Selected 2D NMR correlations for **2** and **3**.

to C-7 at δ_C 45.1 and C-13 at δ_C 65.6. Detailed 2D NMR analysis confirmed the plane structure of **2** as shown in Figure 1. The relative configurations of H-4, H-5, H-8, OH-12, and H-15 were deduced to be α, β, α, β, and β, respectively, according to the cross-peaks of H-4/H-9a, H-4/H-11a, H-5/H-15, H-14b/H-8, and H-14a/H-1a in the ROESY spectrum (Figure 3). Therefore, the structure of compound **2** was determined as 8β-acetoxy-12β-hydroxy-epidihydrolycopodine (**2**) [22].

Compound **3** ($[\alpha]_D^{21.6}$ +132.8) was obtained as a colorless amorphous powder. Its molecular formula was established to be $C_{19}H_{27}NO_4$ by HR-EI-MS at *m/z* 333.1937 $[M]^+$. The ^1H and ^{13}C NMR analyses established the presence of 19 carbon resonances, including two ketonic functions (δ_C 211.9 and 209.7) and an acetyl group (δ_C 170.5, s; 21.0, q), which indicated that **3** should be a lycoflexine-type alkaloid. Further 2D analysis and the NMR data suggested **3** possessed the same planar structure as that of acetyllycoposerramine-U (**9**), a known compound also isolated from this plant [10], and that demonstrated **3** was a stereoisomer of **9**. The ROESY spectrum of **3** showed cross-peaks of H-7/H-11 and H-7/H-17a that indicated H-7 was α-oriented (Figure 3). H-8 was determined to be α-oriented based on the coupling constant between H-8 and H-15, and H-8 and H-7 [dd, 10.5 ($^3J_{H8-H15}$), 4.5 ($^3J_{H8-H7}$)] [15], different with that of **9**. So, the structure of **3** was elucidated as 8β-acetyllycoposerramine-U.

Compound **4** ($[\alpha]_D^{20.2}$ −17.9), a colorless amorphous powder, possessed a molecular formula of $C_{19}H_{24}N_2O_3$ established on the basis of HR-EI-MS at *m/z* 328.1780 $[M]^+$, indicating nine degrees of unsaturation. The ^1H and ^{13}C NMR spectra revealed 19 carbon signals due to three

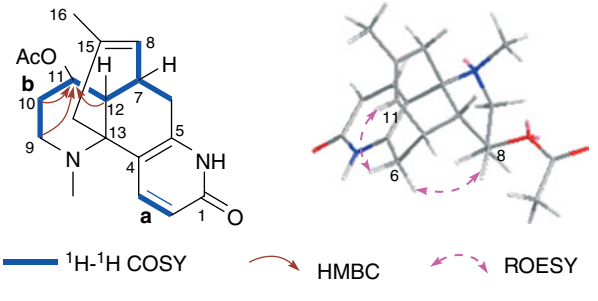

Figure 4. Selected 2D NMR correlations for **4**.

methyls, four methylenes, six methines (three olefinic and one oxygenated), and six quaternary carbons (three olefinic and two carbonyls), which were quite similar to those of casuarine B [23]. The only difference was the presence of one additional acetoxyl group in **4** instead of an hydroxyl group in casuarine B. The acetoxyl group was attached to C-11 on the basis of the HMBC correlations from H-9b at δ_H 2.67–2.68, H-10a at δ_H 1.87–1.89, and H-12 at δ_H 2.15 to C-11 at δ_C 72.4. In the ROESY spectrum, the cross-peaks of H-6a/H-11 and H-8/H-6b were observed that indicated H-11 was α-oriented and H-12 was β-oriented (Figure 4). Thus, the structure of **4** was established as 11β-acetoxyl-*N*-methylhuperzine.

These alkaloids were assayed by measuring NO release against lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophage cells. None of them could inhibit nitric oxide (NO) production.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured on a JASCO P-1020 digital polarimeter (JASCO, Tokyo, Japan). IR spectra were obtained on a Tensor 27 spectrometer (Bruker Optics, Ettlingen, Germany) with KBr pelets. UV spectra were recorded using a Shimadzu UV-2401A spectrophotometer (Shimadzu, Kyoto, Japan). ESI-MS were recorded on an Agilent 6530 Q-Tof spectrometer (Agilent, Palo Alto, CA, USA). EI-MS and HR-EI-MS were measured using a Waters Auto Premier P776 spectrometer (Waters, Milford, MA, USA). 1D and 2D NMR were carried out on Bruker AM-400, DRX-500, or AVANCE III-600 spectrometers with TMS as an internal standard (Bruker Optics). Column chromatography (CC) was carried out over silica gel (100–200 or 200–300 mesh; Qingdao Marine Chemical Co. Ltd, Qingdao, China), MCI gel (CHP 20P, 75–150 μm; Mitsubishi Chemical Corporation, Tokyo, Japan), and Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Sala, Sweden). Thin-layer chromatography was carried out on silica gel 60 F254 on glass plates (Qingdao Marine Chemical, Inc.) using various solvent systems, and spots were visualized by spraying improved Dragendorff's reagent to the silica gel plates.

3.2 Plant material

The whole plants of *P. squarrosus* (7 kg) used in this study were collected from Wenshan, Yunnan Province, China, in June 2012. The plant was identified by Prof. Xiao Cheng at Kunming Institute of Botany, Chinese Academy of Sciences (voucher no. 20120623L2).

3.3 Extraction and isolation

The air-dried whole plants of *P. squarrosus* (7 kg) were extracted with 70% EtOH/H_2O (24 h × 3), and the extract was partitioned between EtOAc and 10% HCl/H_2O. Water-soluble materials, after being adjusted to pH 10 with sat. Na_2CO_3, were then partitioned with $CHCl_3$. $CHCl_3$-soluble materials (18 g) were subjected to reversed-phase MPLC (RP-18) (MeOH/H_2O, 10% → 95%) to give fractions I–V. Fr. III (4.08 g) was chromatographed over a silica gel column ($CHCl_3$/MeOH/H_2O, 200:10:1 → 50:50:1) to give five fractions (Fr. III–I to Fr. III–V). Fr. III–II (1.03 g) was applied to a silica gel column (petroleum ether/acetone/diethylamine, 8:1:1 → 0:1:0) to obtain four fractions. Fr. III–II–III (264 mg) was subjected to repeated silica gel columns ($CHCl_3$/isopropyl alcohol, 1:1 → 0:1 and then petroleum ether/acetone/diethylamine, 8:1:1 → 0:1:0) to afford compounds **5** (5 mg) and **14** (8 mg). Fr. III–III (1.08 g) was separated over a silica gel column (petroleum ether/acetone/diethylamine, 8:1:1 → 0:1:0) and purified by a Sephadex LH-20 column (MeOH) to afford com-

pounds **6** (12 mg), **11** (8 mg), and **16** (43 mg). Fr. IV (13.2 g) was subjected to a silica gel column (petroleum ether/acetone/diethylamine, 8:1:1 → 0:1:0) to give 10 fractions (Fr. IV–I to Fr. IV–X). Fr. IV-VII (8.3 g) was separated over a silica gel column (EtOAc/$CHCl_3$, 20:1 → 1:1) to afford six fractions (Fr. IV–VII–I to Fr. IV–VII–VI). Fr. IV–VII–I (60 mg) was purified by a Sephadex LH-20 column (MeOH) to afford compounds **15** (1 mg) and **18** (6 mg). Fr. IV–VII–III (30 mg) was applied to a silica gel column ($CHCl_3$/isopropyl alcohol, 1:1 → 0:1) to give compound **3** (7 mg). Fr. IV–VII–IV (130 mg) was subjected to a silica gel column ($CHCl_3$/isopropyl alcohol, 1:1 → 0:1) to afford compounds **7** (24 mg) and **13** (5 mg). Fr. IV–VII–V (2.0 g) was chromatographed over repeated silica gel columns ($CHCl_3$/isopropyl alcohol, 1:1 → 0:1 and then petroleum ether/acetone/diethylamine, 8:1:1 → 0:1:0) to give compounds **9** (7 mg), **10** (6 mg), and **12** (11 mg). Fr. IV–VII–VI (180 mg) was purified by a silica gel column ($CHCl_3$/acetone, 1:1 → 0:1) to afford compound **1** (6 mg). Fr. IV–X (2.0 g) was separated over a silica gel column (petroleum ether/acetone/diethylamine, 8:1:1 → 0:1:0) to afford four fractions (Fr. IV–X–I to Fr. IV–X–IV). Fr. IV–X–III (650 mg) was applied to a silica gel column ($CHCl_3$/MeOH, 9:1 → 1:1) to afford compounds **8** (6.4 mg), **17** (7 mg), and **19** (1 mg). Fr. IV–X–IV (100 mg) was separated over a silica gel column ($CHCl_3$/isopropyl alcohol, 1:1 → 0:1) and purified by a Sephadex LH-20 column (MeOH) to afford compounds **2** (12 mg) and **4** (2 mg).

3.3.1 8α-Hydroxylycojapodine A (*1*)

Colorless amorphous powder; $[\alpha]_D^{12.6}$ −49.2 ($c = 1.0$, MeOH); UV (MeOH) λ_{max}(log ε) nm: 201 (3.05); IR (KBr) ν_{max} cm^{-1}: 3441, 1738, and 1686; for ^1H and ^{13}C NMR spectral data, see Table 1; ESI-MS *m/z*: 292 $[M - H]^-$; HR-EI-MS *m/z*: 293.1618 $[M]^+$ (calcd for $C_{16}H_{23}NO_4$, 293.1627).

3.3.2 8β-Acetoxy-12β-hydroxy-epidihydrolycopodine (*2*)

Colorless amorphous powder; $[\alpha]_D^{20.2}$ + 8.61 ($c = 1.1$, MeOH); UV (MeOH) λ_{max} (log ε) nm: 202 (2.78); IR (KBr) ν_{max} cm^{-1}: 3406 and 1725; for ^1H and ^{13}C NMR spectral data, see Table 1; ESI-MS *m/z*: 324 $[M + H]^+$; HR-EI-MS *m/z*: 323.2088 $[M]^+$ (calcd for $C_{18}H_{29}NO_4$, 323.2097).

3.3.3 8β-Acetyllycoposerramine-U (*3*)

Colorless amorphous powder; $[\alpha]_D^{12.6}$ + 132.8 ($c = 1.0$, MeOH); UV (MeOH) λ_{max} (log ε) nm: 203 (3.30); IR (KBr) ν_{max} cm^{-1}: 1736; for ^1H and ^{13}C NMR spectral data see Table 1; ESI-MS *m/z*: 334 $[M + H]^+$; HR-EI-MS *m/z*: 333.1937 $[M]^+$ (calcd for $C_{19}H_{27}NO_4$, 333.1940).

3.3.4 11β-Acetoxyl-N-methylhuperzine B (*4*)

Colorless amorphous powder; $[\alpha]_D^{20.2}$ −17.9 ($c = 0.9$, MeOH); UV (MeOH) λ_{max} (log ε) nm: 201 (3.72), 229 (3.61), 310 (3.47), 386 (1.64); IR (KBr) ν_{max} cm^{-1}: 3429 and 1657; for ^1H and ^{13}C NMR spectral data, see Table 1; ESI-MS *m/z*: 351 $[M + Na]^+$; HR-EI-MS *m/z*: 328.1780 $[M]^+$ (calcd for $C_{19}H_{24}N_2O_3$, 328.1787).

3.4 Bioassay for NO production

Inhibition of NO production and cell viability were constructed in LPS-stimulated RAW 264.7 macrophage cell line. The NO production assay was carried out according to the method described in Ref. [24]. Briefly, the murine monocytic RAW 264.7 macrophages were seeded into 96-well plates (2×10^5 cells/well) containing RPMI-1640 medium (Hyclone, Logan, UT, USA) with

10% fetal bovine serum under a humidified atmosphere of 5% CO_2 at 37°C. After 24 h preincubation, cells were treated with the compounds using the maximum concentration of 25 μm in the presence of 1 μg/ml LPS for 18 h. Each compound was dissolved in DMSO and further diluted in medium to obtain different concentrations. NO production was assessed by adding 100 μl of Griess reagents A and B to 100 μl of each supernatant from LPS or the compound-treated cells in triplicate. After 5 min incubation, the absorbance was measured at 570 nm with a 2104 Envision Multilabel Plate Reader (Perkin-Elmer Life Sciences, Inc., Boston, MA, USA). MG132 (Sigma-Aldrich, St. Louis, MO, USA) was included as a positive control. Cytotoxicity was determined by the MTT assay [25].

Acknowledgments

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