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14-Membered resorcylic acid lactone derivatives with their anti-inflammatory from the fungus *Aspergillus* sp. ZJ-65

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ABSTRACT

Two new 14-membered resorcylic acid lactone derivatives, ascarpins A (**1**) and B (**2**), together with three related known compounds (**3**–**5**) were isolated from the fungus *Aspergillus* sp. ZJ-65, obtaining from the intestine of grass carp. These structures were elucidated on the basis of extensive spectroscopic methods, chemical conversion, and comparison with literature. All isolates were tested for their inhibitory activity against LPS-induced NO production in RAW 264.7 macrophages. Among them, compounds **1**–**4** exhibited potential anti-inflammatory activity with IC_{50} values ranging from 7.6 to 48.3 μM.

1. Introduction

Fungi are well-known for their secondary metabolites with unique structures and prominent biological activities, which play an important role in drug discovery as lead compounds [1–2]. 14-Membered resorcylic acid lactones (RALs) are an class of fungal macrolide metabolites, which possessed a core structure of a *β*-resorcylic acid moiety fused to a 14-membered macrocyclic ring with a methyl substituent at the C-3 position, belong to a subclass of the benzenediol lactone family [3–4]. Up to now, more than130 RALs have been obtained, which were mainly isolated from fungal species of genera *Caryospora*, *Fusarium, Hamigera*, *Hypomyces*, *Paecilomyces* and so on [5]. Selected examples of these macrolides are radicicol [6], zearalenone [7], hypothemycin [8], hamigeromycins C-G [9], and ilyoresorcy C—K [10]. These RALs exhibited a wide spectrum of biological activities such as inhibition of heat shock protein 90 and kinases, antimalarial, antiviral, estrogenic antagonism effects, antibacterial, anticancer, antiparasitic, and antifouling activities [11–14], which were attracted attention of synthetic and medicinal chemists from many research groups worldwide [15–19].

In recent years, we have endeavored to search for structurally unique and biologically interesting metabolites from fungi and a series of fungal bioactive metabolites were discovered, such as citrifurans A-D and asperones A-E [20–21]. As part of our ongoing commitment to discover bioactive metabolites from *Aspergillus* sp. ZJ-65, a fungus isolated from the intestine of grass carp was chemically investigated, resulting in two new RAL derivatives, named ascarpins A-B (**1**–**2**), together with three related known compounds zeaenol (**3**), (5Z)-7-oxozeaenol (**4**), and phenylacetic acid (**5**) (Fig. 1), being isolated. Compounds **1** and **2** represented the first example of RAL derivatives substituted by phenylacetic group. Herein, the details of isolation, structure elucidation, and bioactivity evaluation of these compounds are reported.

2. Experimental

2.1. General experimental procedures

Optical rotations were measured with an Autopol V Plus polarimeter in MeOH (Rudolph, USA). UV spectra were recorded using a UV-2450 visible spectrophotometer (Shimadzu, Japan). IR spectra (KBr disks) were determined by a Bruker Tensor 27 spectrometer (Bruker, Germany). A JASCO J-815 spectropolarimeter was used to measure ECD spectra (JASCO, Japan). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III NMR instrument (Bruker, Germany), with tetramethylsilane (TMS) as an internal standard. High-resolution electrospray ionization mass spectra (HRESIMS) were acquired on Bruker impact II Q-TOF mass spectrometer (Bruker, Germany). Analytical high-performance liquid chromatography (HPLC) was performed on Shimadzu LC-20 CE pump with a SPD-M20A UV detector

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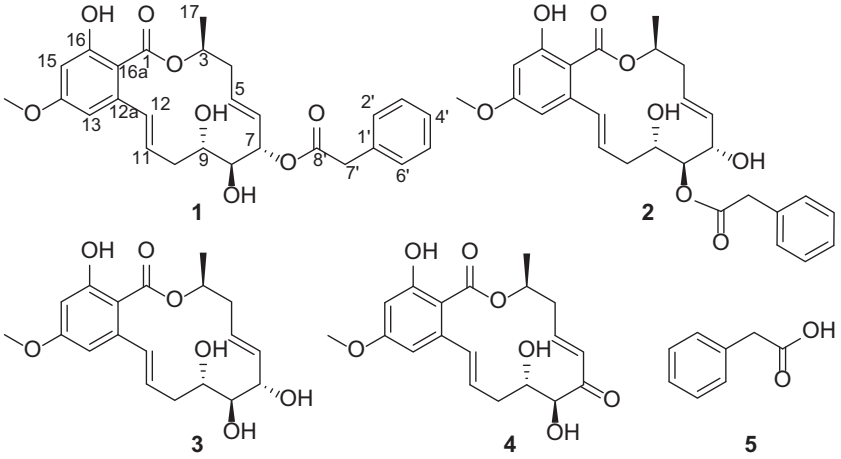

Fig. 1. Structures of compounds **1**–**5**.

(Shimadzu, Japan) and a YMC RP-C_{18} column (5 μm, 4.6 × 250 mm). Preparative high-performance liquid chromatography (Pre-HPLC) was carried out on a Shimadzu LC-6 CE system (Shimadzu, Japan) equipped with a YMC RP-C_{18} column (5 μm, 10 × 250 mm) and flow rate at 3.0 mL/min, detected by a binary channel UV detector at 210 and 254 nm. Column chromatography was performed on silica gel (100–200 and 200–300 mesh, Qingdao Marine Chemical Inc., China) and MCI (50 μm, Mitsubishi, Japan). GF254 plates (Qingdao Marine Chemical Inc., China) was used for TLC. Fractions were monitored by TLC, and the spots were visualized by heating the silica gel plates after spraying with 10% H_2SO_4 in EtOH.

2.2. Fungal material

The fungus was obtained from the intestine of grass carp by plate coating method, which were collected from the reservoir of Longtanzi, Beibei, Chongqing, China, in September 2019. The isolated strain was identified as *Aspergillus* sp. ZJ-65 on the basis of the morphological method and reinforced by 18S rDNA and internal transcribed spacer (ITS) sequences with 100% identity to the known *Aspergillus* sp. (GenBank accession number MT582745.1).

2.3. Extraction and isolation

The strain was cultured on potato dextrose agar (PDA) at 28 °C for 7 days. Then two pieces of the agar (about 1.0 cm3) were added to an Erlenmeyer flask (500 mL) with 200 mL of potato dextrose liquid medium, and the flask was incubated on a rotary shaker at 28 °C and 150 rpm for 5 days to prepare seed culture. Solid fermentation was carried out in 20 Erlenmeyer flasks (1 L), previously sterilized by autoclaving, each containing 200 g rice, 1.0 g glucose, 0.5 g $CuSO_4$•$5H_20$, and 200 mL distilled water. All flasks were incubated at 28 °C for 40 days. The solid cultures were extracted with EtOAc three times at room temperature. The solvent was removed under reduced pressure to yield 52.0 g crude extract.

The crude extract (52.0 g) was subjected to silica gel column chromatography (CC) eluting with a mixture of petroleum ether (60–90 °C) and EtOAc (20:1 to 0:1) with increasing polarity to yield 11 fractions A1-A11, based on TLC. Fr. A7 (5.1 g) was fractionated by MCI eluting with MeOH-H_2O (30:70 to 100:0) to give 10 subfractions A7.1-A7.10. Fr. A7.6 (414.8 mg) was separated preparative HPLC with CH_3OD-H_2O (65:35) to yield compound **3** (112.7 mg). Fr. A8 (6.2 g) was fractionated by MCI eluting with MeOH-H_2O (30:70 to 100:0) to give 12 subfractions A8.1-A8.12. Fr. A8.8 (713.5 mg) was further separated by MCI with MeOH and H_2O (30:70 to 100:0) to give nine subfractions A8.8.1-A8.8.9. Fr. A8.8.5 (110.7 mg) was separated by preparative HPLC with CH_3CN-H_2O (55:45) to yield compound **1** (15.7 mg). Fr. A8.8.6 (98.4 mg) was separated by preparative HPLC with CH_3OD-H_2O (75:25) to yield compound **2** (11.1 mg) and compound **4** (5.9 mg). Fr. A9 (5.4 g) was fractionated by MCI by eluting with MeOH and H_2O (30:70 to 100:0) to give 10 subfractions A9.1-A9.10. Fr. A9.4 (98.4 mg) was separated by preparative HPLC with CH_3OD-H_2O (35:65) to yield compound **5** (58.7 mg).

Table 1
^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectroscopic data of compounds **1** and **2**.

No.	**1** ($CDCl_3$)		**2** (CD_3OD)	
	δ_H	δ_C	δ_H	δ_C
1		171.3		172.5
3	5.26 (1H, m)	71.3	5.33 (1H, m)	72.9
4	2.47 (2H, m)	37.6	2.63 (1H,ddd, 11.8, 5.9, 2.6, 4a) 2.50 (1H, m, 4b)	37.8
5	5.90 (1H,overlap)	131.6	6.04 (1H, dt, 13.0, 5.9)	129.7
6	5.55 (1H,dd, 15.5, 8.0)	126.7	5.65 (1H, overlap)	132.3
7	5.35 (1H,t, 8.0)	76.2	4.06 (1H, t, 8.2)	77.0
8	3.78 (1H, overlap)	75.6	3.67 (1H, overlap)	77.1
9	3.83 (1H, overlap)	73.3	4.92 (1H, overlap)	78.4
10	2.40 (2H, t, 7.0)	35.8	2.42 (2H, m)	32.7
11	5.90 (1H, overlap)	128.9	5.65 (1H, overlap)	129.9
12	7.04 (1H, d, 15.4)	133.6	7.03 (1H, d, 15.3)	134.8
12a		142.9		144.1
13	6.43 (1H, d, 2.5)	107.6	6.29 (1H, d, 2.6)	108.2
14		164.1		165.4
15	6.38 (1H, d, 2.5)	100.1	6.34 (1H, d, 2.6)	100.9
16		165.4		166.4
16a		103.7		105.0
17	1.44 (3H, d, 6.3)	19.4	1.44 (3H, d, 6.3)	19.2
1’		133.8		135.7
2’	7.26–7.35 (1H, overlap)	129.2	7.20–7.32 (1H, overlap)	130.3
3’	7.26–7.35 (1H, overlap)	128.7	7.20–7.32 (1H, overlap)	129.5
4’	7.26–7.35 (1H, overlap)	127.3	7.20–7.32 (1H, overlap)	128.1
5’	7.26–7.35 (1H, overlap)	128.7	7.20–7.32 (1H, overlap)	129.5
6’	7.26–7.35 (1H, overlap)	129.2	7.20–7.32 (1H, overlap)	130.3
7’	3.66 (2H, s)	41.7	3.63 (1H, d, 14.8) 3.70 (1H, d, 14.8)	42.3
8’		170.9		173.4
OCH_3	3.80 (3H, s)	55.4	3.78 (3H, s)	55.9
16-OH	11.96 (1H, s)			

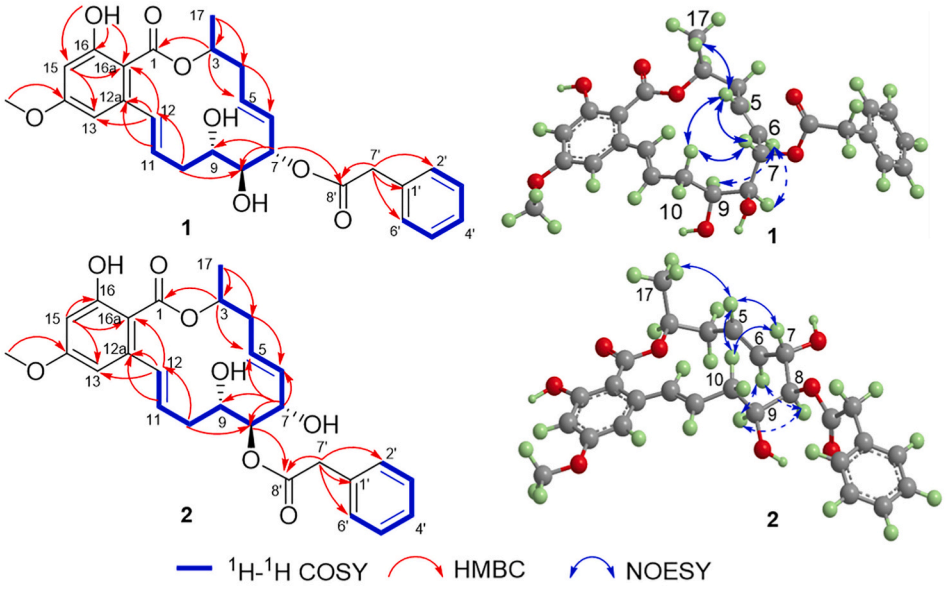

Fig. 2. The key HMBC, ^{1}H—^{1}H COSY, and ROESY correlations of compounds **1** and **2**.

2.4. Spectroscopic data

Ascarpin A (**1**): white amorphous powder; [α]25 D -108 (*c* 0.1, MeOH); UV (MeOH) (log ε) λ_{max} 215 (3.63), 235 (3.86), 255 (3.33), 273 (3.49) nm; IR (KBr) ν_{max}/cm^{-1} 3433, 2941, 1730, 1644, 1606, 1572, 1383, 1355, 1316, 1275, 1161, 1046, 966; ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 233 (+ 49.84), 271 (−29.07) nm; HRESIMS *m/z* 483.2016 [M + H]$^+$ (calcd for $C_{27}H_{31}O_8^+$ 483.2019); ^{1}H NMR and ^{13}C NMR data, see Table 1.

Ascarpin B (**2**): white amorphous powder; [α]25 D -92 (*c* 0.1, MeOH); UV (MeOH) (log ε) λ_{max} 215 (3.72), 235 (3.93), 255 (3.41), 273 (3.57) nm; IR (KBr) νmax/cm^{-1} 3421, 2975, 1730, 1644, 1606, 1575, 1383, 1356, 1315, 1275, 1161, 1039, 968; ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 232 (+ 73.33), 272 (−55.12) nm; HRESIMS *m/z* 483.2020 [M + H]$^+$ (calcd for $C_{27}H_{31}O_8^+$ 483.2019); ^{1}H NMR and ^{13}C NMR data, see Table 1.

Zeaenol (**3**): white amorphous powder; ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 232 (+ 23.49), 270 (−11.80) nm.

2.5. Measurement of NO production

Inhibition of lipopolysaccharide-induced nitric oxide production in RAW 264.7 mouse macrophage cells: cells were evaluated using 96-well plates (1×10^5 cells/well) and allowed to adhere for 2 h at 37 °C in 5% CO_2 in air. Next, the cells were treated with 1 μg/mL LPS for 24 h with or without test compound (5 μg/mL). DMSO was used as the solvent. All compounds were tested at a final concentration of 0.2% (*v*/v) in cell-culture supernatant. NO production was determined from the accumulation of nitrite in the culture supernatant using Griess reagent. The absorbance of the mixture was read at 540 nm using a microplate reader. L-NMMA was used as a positive control in the experiments.

2.6. Cytotoxicity assay

Compounds **1**–**5** were tested for their cytotoxic effects against the mouse macrophages (RAW 264.7 cells) by using the MTT assay. The cytotoxicity evaluations were performed according to the previously described protocol [25].

2.7. Hydrolysis reaction of *1* and *2*

The substrates of **1** (2.0 mg) and **2** (2.1 mg) were dissolved in methanol (100 μL), respectively. Then, solution of sodium hydroxide (200 μL) was added to above solutions to acidify (pH = 10), which were treated on a magnetic stirrer at room temperature for 20 min. Afterward, the HPLC analysis experiment of these samples was performed . The mobile phase consisted of water and methanol. The gradient program was 70–100% methanol in 0–25 min. The flow rate was 1 mL/min and the column temperature was kept constant at 30 °C.

3. Results and discussion

Ascarpin A (**1**) was obtained as white amorphous powder. Its molecular formula, $C_{27}H_{30}O_8$, with 13 degrees of unsaturation, was established on the basis of the HRESIMS at *m/z* 483.2016 [M + H]$^+$ (calcd for $C_{27}H_{31}O_8^+$, 483.2019). This molecular formula was also corroborated by ^{1}H and ^{13}C NMR spectroscopic data. The ^{1}H NMR data (Table 1) showed characteristic signals for two methyl groups at δ_H 3.80 (3H, s) and 1.44 (3H, d, J = 6.3 Hz), two $^4J_{H,H}$ coupled protons at δ_H 6.43 (1H, d, J = 2.5 Hz) and 6.38 (1H, d, J = 2.5 Hz), and a typical mono-substituted phenyl group at δ_H 7.26–7.35 (5H, overlap). On the basis of ^{13}C NMR, DEPT135, and HSQC spectra of **1** (Table 1), it showed resonances for 27 carbons, including two methyl (δ_C 19.4, 55.4), three methylene (35.8, 37.6, and 41.7), 10 methine (four oxygenated at δ_C 71.3, 73.3, 75.6, and 76.2, four olefinic at δ_C 126.7, 128.9, 131.6, and 133.6, and two aromatic at δ_C 100.1 and 107.6), and six nonprotonated (two oxygenated at δ_C 164.1 and 165.4, two carbonyls at δ_C 170.9 and 171.3, and two quaternary at δ_C 103.7 and 142.9), and an extra mono-substituted phenyl group carbons (a quaternary at δ_C 133.8 and five methine carbons at δ_C 127.3, 128.7, 128.7, 129.2, and 129.2). In the 2D NMR spectroscopic data (Fig. 2), the ^{1}H—^{1}H COSY spectrum clearly showed a long spin-systems as the fragment of H_3–17/H-3/H_2–4/H-5/H-6/H-7/H-8/H-9/H_2–10/H-11/H-12, which was further supported by the key HMBC correlations from H_3–17 to C-3 and C-4, from H_2–4 to C-3, C-5, C-6, and C-17, from H-6 to C-4, C-5, C-7, and C-8, from H-7 to C-5, C-6, C-8, and C-9, from H_2–10 to C-8, C-9, C-11, and C-12, and from H-12 to C-10 and C-11. The HMBC correlations from H_2–7′ to C-1′, C-2′, C-6′, and C-8′ suggested that the monosubstituted phenyl, methylene (C-7′), and the carbonyl (C-8′) constructed a phenylacetic group. Further analysis of the chemical shift of C-3 (δ_C 71.3) and C-1 (δ_C 171.3) and the HMBC correlations from H-3 to C-1 indicated that the ester group connected the oxygenated methine between C-1 and C-3. From the above analysis and comparison of the ^{1}H and ^{13}C NMR chemical shifts with literature data suggested that the structure of **1** was similar to the known 14-membered resorcylic acid lactone zeaenol (**3**) [22]. The main difference was that the hydroxy group at C-7 in **3** was replaced by a phenylacetic group in **1**.

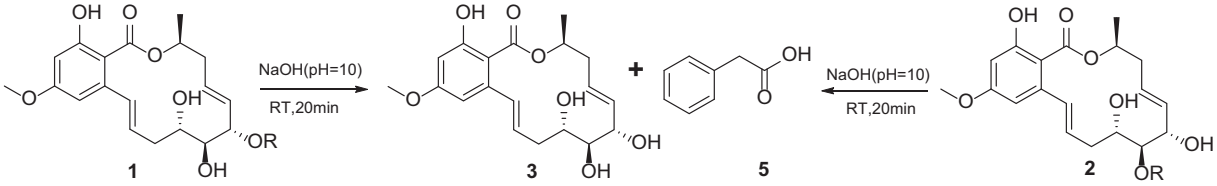

Fig. 3. Hydrolysis reaction of compounds **1** and **2**.

Table 2
The inhibitory effects of compounds **1**–**5** on NO product in RAW 264.7 macrophages.

Compounds	IC_{50} (μM)
1	15.8 ± 1.1
2	7.6 ± 0.9
3	36.2 ± 0.5
4	48.3 ± 1.4
5	>100
L-NAME[a]	55.9 ± 1.9

[a] L-NAME (N^{ω}-nitro-L-arginine methyl ester) was used as a positive control. Data are presented based on three parallel experiments.

The deduce was further corroborated by the key HMBC correlations from H-7 to C-8′, from H-12 to C-12a, C-13, and C-16a, from H-15 to C-13, C-14, C-16, and C-16a, from OH to C-15, C-16, and C-16a, and from OCH_3 to C-14. Thus, the planar structure of **1** (Fig. 1) was established.

The relative configuration of **1** was determined by analysis of coupling constant and ROESY data. Firstly, the characteristic proton resonances of H-7 as a triplet possesses a large coupling constant (J = 8.0 Hz) with H-6 and H-8 indicated that the orientation of H-7 is different from H-6 and H-8. Detailed analysis of the similar structure of **3** with the single-crystal X-ray diffraction experiment data (CCDC number: 1191422) showed that the dihedral angles of H-6/C-6/C-7/H-7 and H-7/C-7/C-8/H-8 were close to 180° [22], which further confirmed above deduce. Secondly, the ROESY correlations (Fig. 2) of H_3–17/H-5, H-5/H-7, H-5/H-10β, H-6/H-8, H-6/H-9, and H-7/H-10β suggested H_3–17 and H-7 were assigned as the same orientation but H-8 and H-9 hold the other orientation. Moreover, the (5*E*,11*E*)-configurations of the two double bonds were determined by the coupling constant value 15.5 and 15.4 Hz for H-5/H-6 and H-11/H-12 respectively. The relative configuration of **1** was therefore predicted to be the same as that of **3** on the basis of above analysis. Additionally, the experimental ECD curve of **1** was similar to that of **3**, while a hydrolysis reaction (Fig. 3; Fig. S24, Supporting Information) showed that **1** was hydrolyzed to produce **3** and **5** under the solution of sodium hydroxide (pH = 10) for 20 min. Hence, the absolute configuration of **1** was determined to be as 5*E*, 11*E*, 3*S*, 7*S*, 8*S*, and *9S*.

Ascarpin B (**2**) was isolated as white amorphous powder, and its molecular formula was also determined to be $C_{27}H_{30}O_8$ by HRESIMS analysis at *m/z* 483.2020 $[M + H]^+$ (calcd for $C_{27}H_{31}O_8^+$, 483.2019), requiring 13 degrees of unsaturation. The ^1H NMR data (Table 1) exhibited signals for two methyl groups, an isolated methylene group, two $^4J_{H,H}$ coupled protons, and a typical monosubstituted phenyl group. The ^{13}C NMR, DEPT135, and HSQC data (Table 1) showed 27 carbon signals, including eight methyl, two methyl, three methylene, 10 methine, six nonprotonated, and an extra typical monosubstituted phenyl group carbons. These spectroscopic data were similar to those of **1** suggested that **2** was also a 14-membered resorcylic acid lactone substituted by phenylacetic group, which was further supported by the ^1H—^1H COSY correlations and HMBC correlations (Fig. 2). However, the HMBC correlations from H-8 to C-8′ revealed that the phenylacetic group moved to C-8 in **2** from C-7 in **1**. The relative configuration of **2** was evidenced to be the same as that of **1**, owing to their similar NOE correlations of H_3–17/H-5, H-5/H-7, H-5/H-10β, H-7/H-10β, H-6/H-8, H-6/H-9, and H-8/H-9 (Fig. 2). Additionally, the ECD data (Fig. S11 and S22) and hydrolysis reaction of **2** (Fig. 3; Fig. S24, Supporting Information) were consistent with that of **1**, which confirmed the absolute configuration of **2** and it was identified as 5*E*, 11*E*, 3*S*, 7*S*, 8*S*, and *9S*.

The known compounds were identified through the analysis of the spectroscopic data and comparison of their data with those in the literature as zeaenol (**3**) [22], (5Z)-7-oxozeaenol (**4**) [23], and phenylacetic acid (**5**) [24].

In addition, the effects of compounds **1**–**5** regarding the inhibition of nitric oxide (NO) production in lipopolysaccharide (LPS)-activated RAW 264.7 mouse peritoneal macrophage cells were evaluated, which were shown in Table 2. Among them, compound **2** showed strong inhibition, while the compounds **1**, **3**, and **4** exhibited moderate inhibitory activity. Moreover, the NO inhibitory activities of **1** and **2** are stronger than that of **3** and **4**. Structurally, compounds **1** and **2** represented the first example of RAL derivatives substituted by phenylacetic group, which indicated that the phenylacetic group as substituent could contribute to enhancing its NO inhibitory activity, especially substituent at C-8. Meanwhile, the cytotoxicity of these compounds against RAW 264.7 cells was also evaluated using the MTT assay. None of the compounds showed significant cytotoxicity at the concentration of 50 μM. These studies will provide references for the development and utilization of RALs.

Declaration of Competing Interest

The authors have declared that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary material of this article is available online, including MS, 1D NMR, 2D NMR, UV, IR, and ECD spectra for compounds **1**–**2**.

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