ORIGINAL ARTICLE

Bioactive Diarylheptanoids from *Alpinia coriandriodora*

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Abstract

Eight new diarylheptanoids, coriandralpinins A–H (**1–8**), were isolated from the rhizomes of *Alpinia coriandriodora*, an edible plant of the ginger family. Their structures, including the absolute configurations, were established by extensive spectroscopic analysis and ECD calculations. Compounds **1–8** have a 1,5-*O*-bridged diarylheptanoid structure featuring polyoxygenated aryl units. When evaluated for intracellular antioxidant activity using *t*-BHP stressed RAW264.7 macrophages, all these compounds scavenged reactive oxygen species (ROS) in a concentration-dependent manner. Compounds **3** and **5** also showed inhibitory activity against NO release in LPS-induced RAW 264.7 cells. Six known flavonols, 7,4'-di-*O*-methylkaempferol, 7-*O*-methylquercetin, 7,4'-di-*O*-methylquercetin, 7,3',4'-tri-*O*-methylquercetin, kaempferol 3-*O*- β -D-(6-*O*- α -L-rhamnopyranosyl)glucopyranoside, and 3-*O*- β -D-glucopyranuronosylquercetin were also isolated and characterized from the rhizomes.

Keywords *Alpinia coriandriodora* · Diarylheptanoid · Antioxidant · Anti-inflammatory

1 Introduction

Metabolism of oxygen is crucial to life for the production of energy to support biological process. As a consequence of the aerobic metabolism, reactive oxygen species (ROS) are continuously generated in all living organisms,

and controlled by several antioxidant mechanisms [1, 2]. However, overproduction and/or mismanagement of ROS may evade cellular antioxidant defense systems, resulting in the general phenomenon of oxidative stress. The redox imbalance leads to cellular damage, which is implicated with inflammatory process and various chronic degeneration diseases such as cancer, cardiovascular disease and diabetes [3–6]. In recent years there has been increasing interest in antioxidants of plant origin [7–10], particularly those from edible plants, and many of these naturally occurring compounds have been shown to possess protective efficacies against oxidative stress and inflammation-related diseases [11–14].

As part of our going effort to isolate and identify antioxidant and anti-inflammatory compounds from edible and medicinal plants, our attention was drawn to *Alpinia coriandriodora* D. Fang (Zingiberaceae), a perennial herb distributed in Guangxi, China. Plants of the genus *Alpinia* are rich in diarylheptanoids, sesquiterpenoids, and monoterpenes, many of which possess antioxidant [15, 16], anti-inflammatory [17], hepatoprotective [18], and anticancer activities [19, 20]. Although *A. coriandriodora* has long been used by local inhabitants as food spices, few chemical investigations on the species have been reported so far. We now present herein the isolation, characterization, and biological

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activities of eight new diarylheptanoids, coriandralpinins A–G (**1–8**) (Fig. 1), from the rhizomes of this plant. The isolation of six known flavonoids is also described.

2 Results and Discussion

The powder of dry *A. coriandriodora* rhizomes was extracted with EtOH. The crude extract was suspended in water and extracted successively with petroleum ether, EtOAc, and *n*-BuOH. The resultant three fractions were separately subjected to column chromatography over silica gel, ODS, and Sephadex LH-20, followed by semi-preparative HPLC, to afford new diarylheptanoids **1–8** (Fig. 1) and known flavonols **9–14** (Fig. S1, Supplementary Material).

Coriandralpinin A (**1**) was obtained as light brown oil. Its HRESIMS showed a pseudo-molecular ion at m/z 435.2009 ($[M + H]^+$), indicating the molecular formula $C_{23}H_{30}O_8$. The ^{13}C NMR spectrum contained signals for 23 carbons including twelve aromatic (four methine and eight non-protonated), four methoxy, four aliphatic methylene, and three aliphatic methine carbons. Combined analysis of the

^1H and ^{13}C NMR data (Tables 1 and 2) with COSY and HSQC spectra revealed the presence of two 3,5-dimethoxy-4-hydroxyphenyl moieties [δ_H 6.41, 6.63 (each 2H, s), 3.84, 3.90 (each 6H, s); δ_C 103.0, 105.2, 56.4, 56.5] and a seven membered aliphatic chain (Fig. 2). In the HMBC spectrum (Fig. 2), correlations of H-1 with C-1', -2', and -6' and of H₂-7 with C-1'', -2'', and -6'' suggested that the two phenyl rings were connected to the alkyl chain terminal carbons C-1 and C-7, respectively. In addition, correlations of H-1/C-5 and H-5/C-1 indicated that C-1 was linked to C-5 via an oxygen atom to form a tetrahydropyran unit. The relative stereochemistry of **1** was elucidated on the basis of proton coupling constants and NOESY correlations. In the ^1H NMR spectrum, H-1 (δ_H 4.26) and H-2ax (δ_H 1.50) appeared as a double doublet ($J = 11.4, 2.0$ Hz) and an apparent quartet ($J = 11.4$ Hz), respectively, suggesting that H-1 and H-3 (δ_H 3.94) are both in axial positions. The remaining oxymethine proton H-5 was also assigned to be axial by the NOE interactions observed for H-5/H-1 and H-5/H-3 (Fig. 2). Based on the established relative configuration, the absolute configuration of **1** was assigned by electronic circular dichroism (ECD) spectrum aided with ECD/TDDFT calculations. The

Fig. 1 Structures of coriandralpinins A–G (**1–8**)

Fig. 2 COSY (bold lines) and key HMBC (arrows) and NOESY (dashed arrows) correlations of **1** (the 3D conformer represents the DFT global energy minimum)

Fig. 3 Comparison between the measured and PBE0/Def2-SVP/PCM (MeOH) calculated ECD spectra of **1** ($\sigma=0.34$, shift = +11 nm)

experimental ECD spectrum of **1** exhibited positive Cotton effects at 242 and 216 nm, which matched well with those of the theoretical spectrum calculated for the 1*S*,3*R*,5*S* isomer (Fig. 3). On the basis of the above analysis, the structure of **1** was established as (1*S*,3*R*,5*S*)-1,5-epoxy-1,7-bis(4-hydroxy-3,5-dimethoxyphenyl)heptan-3-ol.

Coriandralspinins B–E (**2**–**5**) were elucidated to have diarylheptanoid structures closely related to coriandralspinin A (**1**) on the basis of their UV, NMR (Tables 1 and 2), and HRESIMS data. Compound **2** was determined to have a molecular formula containing one CH₂O unit less than **1**. It differed from **1** in that the 3,5-dimethoxy-4-hydroxyphenyl group at C-7 in **1** was replaced by a 4-hydroxy-3-methoxyphenyl group as indicated by an ABX spin system at δ_{H} 6.82 (1H, d, $J=8.0$ Hz), 6.68 (1H, dd, $J=8.0, 1.9$ Hz), and 6.69 (1H, d, $J=1.9$ Hz) for three aromatic protons and a 3H singlet at δ_{H} 3.83 for an aromatic methoxy in the ¹H NMR spectrum. Compounds **3** had a molecular formula with one CH₂ unit less than **2**. Its ¹H NMR spectrum was closely similar to that of **2** except that signals for the C-1 aryl group appeared as two meta-coupled doublets at δ_{H} 6.54 and 6.53 (each 1H, $J=2.0$ Hz) and a 3H singlet at δ_{H} 3.84, indicating a 3,4-dihydroxy-5-methoxyphenyl group. The molecular formula of compound **4** was determined to be C₂₂H₂₈O₈, consisting of a CH₂ unit less than **1**. Its 1D NMR data for the phenyl group at C-7 were similar to those of **1** and the resonances for the C-1 phenyl group were almost identical with those of **3** (Tables 1 and 2), indicating a 3'-*O*-demethyl derivative of **1**. Compound **5** had a molecular formula of C₂₅H₃₂O₉, requiring an additional C₂H₂O unit compared with that of **1**. Its 1D NMR spectra differed from those of **1** in the presence of additional signals [δ_{H} 2.06 (3H, s); δ_{C} 21.4, 170.8] for an acetyl group, which was attached to C-3

via an ester linkage as indicated by the downfield shift of H-3 (δ_{H} 5.02), suggesting a 3-*O*-acetyl derivative of **1**. The above structures deduced for **2**–**5** were also supported by COSY, HSQC, and HMBC spectra. Their stereochemistries were all assigned to be the same as that of **1** on the basis of ¹H NMR coupling constants and NOESY correlations as well as by the similarity of their ECD spectra with that of **1** (Fig. 4). Therefore, the structures of these compound were elucidated as (1*S*,3*R*,5*S*)-1,5-epoxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)heptan-3-ol (**2**), (1*S*,3*R*,5*S*)-1,5-epoxy-1-(3,4-dihydroxy-5-methoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)heptan-3-ol (**3**), (1*S*,3*R*,5*S*)-1,5-epoxy-1-(3,4-dihydroxy-5-methoxyphenyl)-7-(4-hydroxy-3,5-dimethoxyphenyl)heptan-3-ol (**4**), (1*S*,3*R*,5*S*)-3-*O*-acetyl-1,5-epoxy-1,7-bis(4-hydroxy-3,5-dimethoxyphenyl)heptan-3-ol (**5**). It is noted that two diarylheptanoids of unknown absolute configurations isolated from ginger [21] had been reported to possess the same planar and relative stereochemical structures as **2** and **3** and they had optical rotations ($[\alpha]_{\text{D}}$) with values similar but sign opposite to those of **2** and **3**, indicating the reported compounds are likely the enantiomers of our compounds.

Coriandralspinin F (**6**) had a molecular formula of C₂₃H₂₈O₉ according to HRESIMS data. Its UV spectrum was largely similar to those of **1**–**5** but differed in that the absorption maximum at the longest wavelength was significantly red-shifted (301 nm vs 271–280 nm), suggesting the presence of a chromophore with extended conjugated system. This finding was consistent with the ¹H and ¹³C NMR data (Tables 1 and 2), which were comparable to those of **1** except the carbon signal indicating the presence of a conjugated ketone carbonyl (δ_{C} 199.5) and the absence of proton and carbon resonances for C-7 methylene. Detailed analysis

Fig. 4 Comparison of the ECD spectra measured for **1**–**5**

Fig. 5 Comparison of the measured ECD spectra of **6** and **7** with PBE0/TZVP/PCM(MeOH) calculated ECD spectra of (1*R*,3*S*,5*S*)- and (1*S*,3*R*,5*R*)-**6** ($\sigma=0.38$, shift = −11 nm)

of the 1D and 2D NMR data readily derived a structure of 7-keto derivative of **1**, including the relative stereochemistry. As the experimental ECD spectrum of **6** was significantly different from the spectrum of **1**, theoretical computations of ECD spectrum were carried out in order to solve the absolute stereochemistry. As a result (Fig. 5), chiral carbons in **6** were shown to be inverted relative to those in **1–5**, designating this compound as 1*R*,3*S*,5*S*. Coriandrpinin G (**7**) was a 3'-*O*-demethyl derivative of **6** as elucidated by analysis of the 1D NMR (Tables 1 and 2), 2D NMR, and HRESIMS data. Its absolute stereochemistry was assigned to be the same as that of **6** based on the nearly parallel experimental ECD curves of the two compounds (Fig. 5). Thus, the structures of compounds **6** and **7** were established to be (1*R*,3*S*,5*S*)-1,5-epoxy-3-hydroxy-1,7-bis(4-hydroxy-3,5-dimethoxyphenyl)heptan-7-one and (1*R*,3*S*,5*S*)-1,5-epoxy-3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-7-(3,4-dihydroxy-5-methoxyphenyl)heptan-7-one, respectively.

The planar structure of the last diarylheptanoid, coriandrpinin H (**8**), was established to be 7-methoxylated **1** by analysis of NMR and MS data. Different from the other analogues, compound **8** had one more chiral center C-7, which brought a challenge of solving its stereochemistry. Analysis of proton coupling constants (Table 1) and NOESY data readily assigned the relative configuration of tetrahydropyran ring to be the same as that in **1–7**, but gave no clear information for the configuration at C-7. In order to assign the absolute configuration of **8**, ECD/TDDFT calculations were carried out for 1*S*,3*R*,5*R*,7*R* and 1*S*,3*R*,5*R*,7*S* stereoisomers. Unfortunately, the simulated ECD spectrum of (1*S*,3*R*,5*R*,7*S*)-**8** and the mirror-image of the calculated spectrum for (1*S*,3*R*,5*R*,7*R*)-**8** were both in good agreement with the measured spectrum of **8** (Fig. 6). To

Fig. 6 Comparison between the ECD spectra measured for **8** and PBE0/TZVP/PCM calculated for four possible stereoisomers of **8** ($\sigma=0.38$, shift = −2 nm)

further define the absolute configuration, ^{13}C NMR shifts of (1*S*,3*R*,5*R*,7*R*)-**8** and (1*S*,3*R*,5*R*,7*S*)-**8** were calculated using the gauge including atomic orbitals (GIAO) method at the mPW1PW91/6–311 + G(d,p)/PCM level of theory. The calculated ^{13}C NMR data of (1*S*,3*R*,5*R*,7*R*)-**8** showed a better match with the measured data of **8** (DP4 + probability: 98.4%) than (1*S*,3*R*,5*R*,7*S*)-**8** (DP4 + probability: 1.6%) (Fig. 7), suggesting a 1*S*,3*R*,5*R*,7*R* or 1*R*,3*S*,5*S*,7*S* configuration. This, together with the results of ECD simulations, allowed designation of **8** as 1*R*,3*S*,5*S*,7*S*. In consequence, the structure of **8** was determined as (1*R*,3*S*,5*S*,7*S*)-1,5-epoxy-7-methoxy-1,7-bis(4-hydroxy-3,5-dimethoxyphenyl)heptan-3-ol.

The isolated known flavonoids were identified to be 7,4'-di-*O*-methylkaempferol (**9**) [22], 7-*O*-methylquercetin (**10**) [23], 7,4'-di-*O*-methylquercetin (**11**) [24], 7,3',4'-tri-*O*-methyl-quercetin (**12**) [25], kaempferol 3-*O*- β -D-(6-*O*- α -L-rhamnopyranosyl)glucopyranoside (**13**) [26], and 3-*O*- β -D-glucopyranuronosylquercetin (**14**) [27] (Fig. S1, Supplementary Material) by interpretation of their spectroscopic data as well as by comparison of the data with reported values in literatures.

Compounds **1–8** were evaluated for antioxidant and anti-inflammatory activities in respect that the two activities are of the most common and interesting biological properties of diarylheptanoids [28–30]. The antioxidant activity evaluation was conducted using a more physiologically relevant method, the cellular antioxidant activity (CAA) assay [29, 30], with RAW 264.7 macrophages as the test cells. The concentrations of compounds used in the assay were 50 μM and lowers according to cell viability assay by MTT method, which showed that **1–8** had no

Fig. 7 Linear regression analysis of the calculated ^{13}C NMR shifts of two possible stereoisomers against the measured shifts of **8** and the DP4+ probability for **8** to be the stereoisomers

observable toxicity to RAW 264.7 cells at the concentration up to 100 μM . As indicated in Fig. 8 and Table 3, all these compounds were capable of significantly decreasing *t*-BHP-induced ROS production in RAW 264.7 cells in a concentration-dependent manner (Fig. 8), although none of them was more potent than the positive control curcumin. Among them, 3'- or 3''-OH bearing **3**, **4**, and **7** exhibited better activity (IC_{50} : 12.0–18.0 μM) than their corresponding 3'- or 3''-*O*-methyl derivatives **2**, **5**, and **6** (Table 3). Besides, the change of 7-keto carbonyl to the methoxylated methine was shown to increase the activity (**6** vs **8**).

The potential anti-inflammatory activity of compounds **1**–**8** was evaluated by measuring their inhibitory effects on nitric oxide (NO) production in lipopolysaccharide (LPS)-induced RAW 264.7 cells (Table 3). Among these diarylheptanoids, compounds **3** and **5** exhibited inhibitory activity against NO release with IC_{50} values of 36.9 and 34.1 μM , respectively, which were comparable to that of the positive drug control dexamethasone (IC_{50} : 33.6 μM). However, other isolated analogues were inactive in the assay ($\text{IC}_{50} > 50 \mu\text{M}$).

In summary, phytochemical analysis of *A. Coriandriodora* rhizomes led to the characterization of a group of

Fig. 8 Concentration-dependent inhibition of *t*-BHP-induced ROS production in RAW264.7 cells by compounds **1**–**8** and the positive control curcumin ($^*P < 0.05$ vs *t*-BHP alone)

Table 1 ^1H NMR (500 MHz) data for compounds **1–8**

position	1 ^a	2 ^a	3 ^b	4 ^b	5 ^a	6 ^b	7 ^b	8 ^b
1	4.26 dd (11.4, 2.0)	4.26 dd (11.4, 2.0)	4.19 dd (11.4, 1.9)	4.18 dd (11.4, 1.9)	4.33 dd (11.5, 2.0)	4.34 dd (11.4, 1.9)	4.32 d (10.1)	4.30–4.36 m
2	ax 1.50 q (11.4) eq 2.20 ddt (12.5, 4.3, 2.0)	ax 1.51 q (11.4) eq 2.20 ddt (12.5, 4.3, 2.0)	ax 1.41 q (11.4) eq 2.08 ddt (12.5, 4.3, 2.0)	ax 1.41 q (11.4) eq 2.08 ddt (12.4, 4.2, 1.9)	ax 1.59 q (11.7) eq 2.23 br d (12.7, 4.1, 1.8)	ax 1.36–1.46 m eq 2.11–2.17 m	ax 1.34–1.44 m eq 2.10–2.18 m	ax 1.46 q (11.6) eq 2.13 ddt (12.4, 4.0, 1.6)
3	3.94 m	3.95 m	3.81 m	3.82 m	5.02 m	3.93 m	3.95 m	3.90 m
4	ax 1.33 q (11.4) eq 2.03 ddt (12.2, 4.1, 1.8)	ax 1.33 q (11.4) eq 2.03 ddt (12.3, 4.1, 1.9)	ax 1.23 q (11.5) eq 1.95 ddt (12.4, 4.4, 1.9)	ax 1.23 q (11.3) eq 1.94 ddt (12.3, 4.3, 1.9)	ax 1.44 q (11.6) eq 2.09 m	ax 1.36–1.46 m eq 2.11–2.17 m	ax 1.34–1.44 m eq 2.10–2.18 m	ax 1.24 q (11.6) eq 2.01 ddt (12.4, 4.0, 1.7)
5	3.45 m	3.45 m	3.42 m	3.40 m	3.51 m	4.10 m	4.10 m	3.76 m
6	1.98 m 1.81 m	1.98 m 1.80 m	1.87 m 1.75 m	1.75 m 1.87 m	1.99 m 1.81 m	3.36 dd (15.2, 7.1) 3.08 dd (15.2, 5.0)	3.35 dd (15.1, 7.1) 2.98 dd (15.1, 5.2)	1.93 m 1.83 m
7	2.67–2.75 m	2.64–2.77 m	2.61–2.72 m	2.61–2.71 m	2.61–2.73 m			4.30–4.36 m
2'	6.63 s	6.62 s	6.54 d (2.0)	6.55 d (1.9)	6.61 s	6.54 s	6.54 s	6.67 s
6'	6.63 s	6.62 s	6.53 d (2.0)	6.53 d (1.9)	6.61 s	6.54 s	6.54 s	6.67 s
2''	6.41 s	6.69 d (1.9)	6.76 d (2.0)	6.45 s	6.40 s	7.36 s	7.23 d (2.0)	6.58 s
3''		6.82 d (8.0)	6.69 d (8.0)					
6''	6.41 s	6.68 dd (8.0, 1.9)	6.62 dd (8.0, 2.0)	6.45 s	6.40 s	7.36 s	7.20 d (2.0)	6.58 s
7-OCH ₃								3.19 s
3'-OCH ₃	3.90 s	3.90 s			3.90 s	3.85 s	3.75 s	3.85 s
5'-OCH ₃	3.90 s	3.90 s	3.84 s	3.83 s	3.90 s	3.85 s	3.75 s	3.85 s
3''-OCH ₃	3.84 s			3.77 s	3.84 s	3.74 s		3.81 s
5''-OCH ₃	3.84 s	3.83 s	3.78 s	3.77 s	3.84 s	3.74 s	3.84 s	3.81 s
CH ₃ CO					2.06 s			

^aCDCl₃ used as solvent^bCD₃OD used as solvent

unique 1,5-*O*-bridged diarylheptanoids, coriandralpinins A–H (**1–8**). These compounds exhibited remarkable intracellular antioxidant activity in concentration-dependent manner. Compounds **3** and **5** also inhibited NO release in LPS-induced RAW 264.7 cells. The results suggested that the edible plant *A. coriandriodora* is a potential source for dietary supplements.

3 Experimental Section

3.1 General Experimental Procedures

Optical rotations were obtained on a Perkin-Elmer 341 polarimeter with MeOH as solvent. UV and ECD spectra were recorded in MeOH with a Chirascan CD spectrometer (Applied Photophysics LTD., England). ^1H NMR, ^{13}C NMR, and 2D NMR spectra were recorded in chloroform-*d*

or methanol-*d*₄ on a Bruker AVIII 500 M instrument for ^1H at 500 and for ^{13}C at 125 MHz using the residual solvent peak as reference. High-resolution electrospray ionization mass spectrometry (HRESIMS) was obtained on Bruker maXis Q-TOF mass spectrometer. ESIMS data were obtained on an MDS SCIEX API 2000 LC/MS instrument (SCIEX, Toronto, Canada). HRESIMS data were obtained on a Bruker Bio TOF IIIQ mass spectrometer (Bruker Daltonics, Billerica, MA, U.S.A.). Preparative HPLC was performed with an HPLC system equipped with a Shimadzu LC-6AD pump (Shimadzu, Kyoto, Japan) using a YMC-pack ODS-A column (5 μm , 10 $\times$ 250 mm, YMC, Kyoto, Japan). For column chromatography, silica gel 60 (100–200 mesh, Qingdao Marine Chemical Ltd., Qingdao, China) and YMC ODS (75 μm , YMC, Kyoto, Japan) were used. TLC was performed using HSGF254 silica gel plates (Yantai Jiangyou Silica Gel Development Co. Ltd., Yantai, China).

Table 2 ^{13}C NMR (125 MHz) data for compounds **1–8**

Position	1 ^a	2 ^a	3 ^b	4 ^b	5 ^a	6 ^b	7 ^b	8 ^b
1	77.7	77.6	79.0	79.0	77.6	79.1	78.9	79.2
2	43.1	42.9	43.7	43.8	39.3	43.6	43.7	43.7
3	68.6	68.7	69.0	69.0	70.9	68.7	68.7	69.0
4	41.0	40.9	41.9	41.8	37.1	41.7	41.8	42.3
5	75.0	75.0	76.2	76.2	75.0	74.7	74.7	74.3
6	37.9	37.9	39.1	39.0	37.9	45.3	45.2	46.2
7	32.0	31.5	32.3	32.8	32.0	199.5	199.6	81.8
1'	133.4	133.4	134.6	134.5	133.0	134.4	134.4	134.5
2'	103.0	103.1	108.0	108.0	103.0	104.5	104.3	104.8
3'	147.1	147.1	146.4	146.4	147.1	148.9	149.0	149.1
4'	134.3	134.0	134.5	134.2	134.3	136.5	135.8	136.0
5'	147.1	147.1	149.5	149.4	147.1	148.9	149.0	149.1
6'	103.0	103.1	102.8	102.7	103.0	104.5	104.3	104.8
1''	133.2	134.3	135.0	134.5	133.1	129.7	129.8	134.3
2''	105.2	111.2	113.3	106.7	105.2	107.8	111.6	104.8
3''	147.1	114.3	116.1	149.1	147.1	149.0	146.3	149.4
4''	132.9	143.8	145.5	134.6	133.0	142.6	141.2	135.9
5''	147.1	146.5	148.8	149.1	147.1	149.0	149.2	149.4
6''	105.2	121.1	121.8	106.7	105.2	107.8	105.3	104.8
7-OCH ₃								56.7
3'-OCH ₃	56.5	56.5			56.5	56.8	56.7	56.8
5'-OCH ₃	56.5	56.5	56.6	56.6	56.5	56.8	56.7	56.8
3''-OCH ₃	56.4			56.7	56.4	56.7		56.7
5''-OCH ₃	56.4	56.0	56.3	56.7	56.4	56.7	56.7	56.7
CH ₃ CO					170.8			
CH ₃ CO					21.4			

^aCDCl₃ used as solvent^bCD₃OD used as solvent**Table 3** Inhibitory activity of compounds **1–8** against *t*-BHP-induced ROS and LPS-induced NO production in RAW264.7 cells

compound	Inhibition of ROS (IC ₅₀ , μM) ^a	Inhibition of NO (IC ₅₀ , μM) ^a
1	43.0 ± 1.5	> 50
2	31.1 ± 2.6	> 50
3	18.0 ± 0.7	36.9 ± 1.1
4	17.6 ± 1.0	> 50
5	31.0 ± 3.3	34.1 ± 0.6
6	> 50	> 50
7	12.0 ± 2.1	> 50
8	29.9 ± 1.8	> 50
Curcumin	8.6 ± 0.4	
Dexamethasone		33.6 ± 1.5

^aData are presented as mean ± SD (*n* = 3)

3.2 Plant Material

The rhizomes of *A. Coriandriodora* were purchased from Nanning, Guangxi, China, in January 2018. A voucher specimen (specimen number SC-42–3–7) was deposited at the Herbarium of South China Botanical Garden, Chinese Academy of Sciences.

3.3 Extraction and Isolation

The fresh rhisomes of *A. Coriandriodora* (1.55 kg), after being dried at 50 °C in an oven, were crushed into powder (260 g) and then extracted with 95% EtOH for 48 h (×3). The crude extract (58 g) was suspended in water and extracted successively with petroleum ether (PE), EtOAc, and *n*-BuOH for three times each. The PE-soluble fraction (13 g) was subjected to silica gel column chromatography (CC) using gradient PE-acetone mixtures (v/v, 100:0–60:40) to obtain ten fractions (Fr. A1 to Fr. A10). Fr. A5 (470 mg) was separated by Sephadex LH-20 CC using PE-CH₂Cl₂-MeOH (1:1:1) to afford

compound **9** (150 mg). Fr. A10 was applied to ODS CC using MeOH-H₂O (v/v, 30:70–100:0) to give ten subfractions (Fr. A10-1 to Fr. A10-10). Fr. A10-9 (12 mg) and Fr. A10-10 (30 mg) were further separated by Sephadex LH-20 CC using PE-CH₂Cl₂-MeOH (1:1:1) to obtain **11** (3 mg) and **12** (25 mg), respectively. Fr. A10-5 (6 mg) was purified by preparative HPLC using 30% MeCN to afford **10** (1 mg, t_R = 25.6 min). The EtOAc-soluble fraction (11.42 g) was subjected to silica gel CC, eluted with gradient CH₂Cl₂-MeOH mixtures (v/v, 100:0 to 50:50), to afford eleven fractions (Fr. B1 to Fr. B11). Fr. B5 (271 mg) was chromatographed on a Sephadex LH-20 column using PE-CH₂Cl₂-MeOH (1:1:1) to yield **1** (244 mg). Fr. B6 (1.17 g) was further applied to ODS CC using MeOH-H₂O (v/v, 1:9 to 10:0) to yield eleven subfractions (Fr. B6-1 to Fr. B6-11). Fr. B6-4 was subjected to Sephadex LH-20 CC using PE-CH₂Cl₂-MeOH (1:1:1) followed by preparative HPLC to yield **6** (2 mg, t_R = 36.6 min) and **2** (9 mg, t_R = 95.0 min) using 20% CH₃CN and **5** (5 mg, t_R = 79.6 min) using 34% CH₃CN. Fr. B8 (3.42 g) was subjected to ODS CC using MeOH-H₂O (v/v, 1:9 to 10:0) to give twelve subfractions (Fr. B8-1 to Fr. B8-12). Fr. B8-4 was further separated by HPLC using 17% CH₃CN to afford **7** (10 mg, t_R = 27.1 min). Fr. B8-5 was subjected to Sephadex LH-20 CC using PE-CH₂Cl₂-MeOH (1:1:1) followed by preparative HPLC using 20% CH₃CN to yield **8** (3 mg, t_R = 51.1 min), **4** (76 mg, t_R = 45.3 min), and **3** (11 mg, t_R = 54.1 min). The *n*-BuOH-soluble fraction (1 g) was subjected ODS CC using MeOH-H₂O (v/v, 1:9–3:7) to give three fractions (Fr. C1 to Fr. C3). Fr. C1 (141 mg) was separated by preparative HPLC using 22% MeCN to afford **13** (22 mg, t_R = 11.2 min) and **14** (8 mg, t_R = 13.0 min).

Coriandralpinin A (1): light brown oil; $[\alpha]_D^{20}$ + 51.1 (c 0.33, MeOH); UV (MeOH) $\lambda_{\max}$ nm (log ϵ): 206 (3.93), 230 (3.12), 272 (2.30); CD (MeOH) $\Delta\epsilon$ 219 (+1.97), 239 (+2.63); ¹H and ¹³C NMR data were depicted Tables 1 and 2. HRESIMS m/z 435.2009 [M+H]⁺ (calcd for C₂₃H₃₁O₈, 435.2014), m/z 457.1836 [M+Na]⁺ (calcd for C₂₃H₃₀NaO₈, 457.1833).

Coriandralpinin B (2): light brown oil, $[\alpha]_D^{20}$ + 54.5 (c 0.70, MeOH). UV (MeOH) $\lambda_{\max}$ nm (log ϵ): 202 (3.96), 230 (3.20), 280 (2.72); CD (MeOH) $\Delta\epsilon$ 207 (+6.07), 236 (+3.31); ¹H and ¹³C NMR data were depicted Tables 1 and 2. (+)-HRESIMS: m/z 405.1914 [M+H]⁺ (calcd for C₂₂H₂₉O₇, 405.1908), m/z 427.1736 [M+Na]⁺ (calcd for C₂₂H₂₈NaO₇, 427.1728).

Coriandralpinin C (3): light yellow oil, $[\alpha]_D^{20}$ + 54.9 (c 0.99, MeOH). UV (MeOH) $\lambda_{\max}$ nm (log ϵ): 201 (4.00), 230 (3.24), 279 (2.71); CD (MeOH) $\Delta\epsilon$ 212 (+5.59), 236 (+2.57); ¹H and ¹³C NMR data were depicted Tables 1 and 2. (+)-HRESIMS: m/z 391.1748 [M+H]⁺ (calcd for C₂₁H₂₇O₇, 391.1752), m/z 413.1571 [M+Na]⁺ (calcd for C₂₁H₂₆NaO₇, 413.1571).

Coriandralpinin D (4): orange oil, $[\alpha]_D^{20}$ + 56.4 (c 0.25, MeOH). UV (MeOH) $\lambda_{\max}$ nm (log ϵ): 205 (3.97), 229 (3.18), 271 (2.31); CD (MeOH) $\Delta\epsilon$ 214 (+4.89), 237 (+2.82); ¹H and ¹³C NMR data were depicted Tables 1 and 2. (+)-HRESIMS: m/z 421.1851 [M+H]⁺ (calcd for C₂₂H₂₉O₈, 421.1857), m/z 443.1674 [M+Na]⁺ (calcd for C₂₂H₂₈NaO₈, 443.1677).

Coriandralpinin E (5): light yellow oil, $[\alpha]_D^{20}$ + 34.8 (c 0.56, MeOH). UV (MeOH) $\lambda_{\max}$ nm (log ϵ): 206 (3.90), 230 (3.10), 271 (2.30); CD (MeOH) $\Delta\epsilon$ 223 (+0.42), 241 (+1.83); ¹H and ¹³C NMR data were depicted Tables 1 and 2. (+)-HRESIMS: m/z 477.2114 [M+H]⁺ (calcd for C₂₅H₃₃O₉, 477.2120), m/z 499.1934 [M+Na]⁺ (calcd for C₂₅H₃₂NaO₉, 499.1939).

Coriandralpinin F (6): light brown oil, $[\alpha]_D^{20}$ + 10.3 (c 0.18, MeOH). UV (MeOH) $\lambda_{\max}$ nm (log ϵ): 206 (3.47), 225 (3.06), 301 (2.72); CD (MeOH) $\Delta\epsilon$ 210 (−1.03), 285 (−0.24), 338 (+0.14); ¹H and ¹³C NMR data were depicted Tables 1 and 2. (+)-HRESIMS: m/z 449.1804 [M+H]⁺ (calcd for C₂₃H₂₉O₉, 449.1807), m/z 471.1623 [M+Na]⁺ (calcd for C₂₃H₂₈NaO₉, 471.1626).

Coriandralpinin G (7): yellow oil, $[\alpha]_D^{20}$ + 19.8 (c 0.81, MeOH). UV (MeOH) $\lambda_{\max}$ nm (log ϵ): 206 (3.77), 225 (3.33), 301 (2.72); CD (MeOH) $\Delta\epsilon$ 214 (−0.62), 287 (−0.81), 333 (+0.38); ¹H and ¹³C NMR data were depicted Tables 1 and 2. (+)-HRESIMS: m/z 435.1658 [M+H]⁺ (calcd for C₂₂H₂₇O₉, 435.1650), m/z 457.1466 [M+Na]⁺ (calcd for C₂₂H₂₆NaO₉, 457.1470).

Coriandralpinin H (8): light brown oil, $[\alpha]_D^{20}$ + 34.9 (c 0.25, MeOH). UV (MeOH) $\lambda_{\max}$ nm (log ϵ): 206 (3.92), 235 (3.10), 271 (2.31); ¹H and ¹³C NMR data were depicted Tables 1 and 2. (+)-HRESIMS: m/z 487.1942 [M+Na]⁺ (calcd for C₂₄H₃₂NaO₉, 487.1939), m/z 951.3994 [2 M+Na]⁺ (calcd for C₄₈H₆₄NaO₁₈, 951.3985).

3.4 Cell Viability Assay

The murine macrophage RAW 264.7 cell line was obtained from Kunming Institute of Zoology, Chinese Academy of Sciences (Kunming, China). The cells were cultured in DMEM medium supplemented with 10% heated-inactivated fetal bovine serum in a 37 °C, 5% CO₂ incubator. Compounds **1–8**, curcumin, and *t*-BHP were assessed for cytotoxicity against RAW 264.7 cells at various concentrations (100, 50, 10, and 2 μM) by MTT method as previously described [31].

3.5 Cellular Antioxidant Activity Assay

In the MTT cell viability assay, 50 μM of *t*-BHP (Sigma-Aldrich, USA, TBH70X) treatment for 3 h provoked about 60% of cell death and this condition was selected for the subsequent experiments as reported [29, 30]. Briefly, RAW

264.7 cells (4×10^4 cells/well) were seeded into a black 96-well plate and allowed to grow for 24 h, then treated with either compounds (100, 50, 25, 12.5, and 6.25 μM) or the positive control curcumin (20, 10, 5, 2.5, and 1.25 μM) for 24 h. After stained with 20 μM DCFH-DA (Sigma, USA) for 1 h in darkness, the cells were exposed to 50 μM *t*-BHP for 1 h to induce ROS generation. The supernatants of cell cultures were measured for intracellular ROS levels using the fluorescence intensity at excitation wavelength of 485 nm and the emission wavelength of 530 nm by microplate reader (Tecan Group Ltd., Switzerland).

3.6 Anti-Inflammatory Activity Evaluation

The in vitro anti-inflammatory activity was evaluated by measuring the inhibitory effects of compounds on NO production in LPS-stimulated RAW 264.7 macrophages as previously described [32]. Briefly, the supernatants of cells were obtained as described above and RAW 264.7 cells were pretreated with different concentrations of compounds **1–8** (50, 25, 12.5, 6.25, and 3.125 μM) at 37 °C for 1 h, followed by stimulated with LPS (0.1 $\mu\text{g}/\text{ml}$) for 24 h. DMSO (0.1%) and dexamethasone (50, 25, 12.5, 6.25 and 3.125 μM) were used as vehicle and positive controls, respectively. The levels of NO were determined using commercial NO assay kit (Beyotime Institute of Biotechnology, China). 50 μL of Griess reagent I and 50 μL of Griess reagent II were added to 100 μL of the supernatants of cells ($9 \times 10^5/\text{mL}$).

3.7 Computational Methods

Molecular Merck force field (MMFF) and DFT/TDDFT calculations were performed with Spartan'14 software package (Wavefunction Inc., Irvine, CA, USA) and Gaussian09 program package [33], respectively. The structures, (1*S*,3*R*,5*S*)-**1**, (1*S*,3*R*,5*R*)-**6**, (1*S*,3*R*,5*R*,7*R*)-**8**, and (1*S*,3*R*,5*R*,7*S*)-**8**, were applied to the theoretical calculations. MMFF conformational search generated low-energy conformers within a 10 kcal/mol energy window were subjected to geometry optimization using DFT method at the B3LYP/def2-SVP [34] level of theory with the solvent model PCM for MeOH. Frequency calculations were run at the same level to verify that each optimized conformer was a true minimum and to estimate their relative thermal free energies (ΔG). The optimized minima (Table S1, Supplementary Material) within the relative energies of 4.0 kcal/mol were subjected to the higher level of energy calculations at the M06-2X [35]/def2-TZVP [34] level with the solvent model SMD for MeOH. The TDDFT calculations were performed using the hybrid PBE0 (PBE1PBE) [36, 37] and M06-2X functionals, and Ahlrichs' basis sets def2-SVP and TZVP [38] with the PCM for MeOH. The number of excited states per each molecule was 42 for

all compounds. The ECD spectra were generated by the program SpecDis [39] using a Gaussian band shape from rotational strengths. The final calculated spectra were generated by averaging calculated spectra of the low-energy conformers according to the Boltzmann weighting of each conformer in MeOH solution. The theoretical ECD spectra of (1*R*,3*S*,5*R*)-**1**, (1*R*,3*S*,5*S*)-**6**, (1*R*,3*S*,5*S*,7*S*)-**8**, and (1*R*,3*S*,5*S*,7*R*)-**8**, were obtained by mirror-inversion of the calculated spectra for (1*S*,3*R*,5*S*)-**1**, (1*S*,3*R*,5*R*)-**6**, (1*S*,3*R*,5*R*,7*R*)-**8**, and (1*S*,3*R*,6*R*,7*S*)-**8**, respectively.

For calculations of the ^{13}C NMR shifts of **8**, low-energy conformers of the stereoisomers, (1*S*,3*R*,5*R*,7*R*)-**8** and (1*S*,3*R*,5*R*,7*S*)-**8**, obtained in above ECD simulations, were subjected to NMR calculations using the gauge including atomic orbitals (GIAO) method [40, 41, 42] at the mPW1PW91/6–311 + G(d,p)/PCM level [43]. The unscaled chemical shifts (δ_u) were computed using TMS as reference standard according to $\delta_u = \sigma_0 - \sigma^x$ (where σ^x is the Boltzmann averaged shielding tensor and σ_0 is the shielding tensor of TMS computed at the same level employed for σ^x). The Boltzmann averaging was done at 298.15 K using the relative energies obtained from the single-point NMR calculations [44, 45]. The goodness of fit between the predicted ^{13}C NMR data of the two stereoisomers and the experimental shifts of compound **8** were evaluated by the improved DP4 probability (DP4+) [44, 45].

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Compliance with Ethical Standards

Conflict of interest The authors declare no competing financial interest.

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