



# Three new polyketides from a mangrove-derived fungus *Colletotrichum gloeosporioides*

You-Ping Luo<sup>1,2</sup> · Cai-Juan Zheng<sup>1,2</sup> · Guang-Ying Chen<sup>1,2</sup> · Xiao-Ping Song<sup>1,2</sup> · Zhe Wang<sup>2</sup>

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## Abstract

Three new polyketides, (2*S*)-2,3-dihydro-5,6-dihydroxy-2-methyl-4*H*-1-benzopyran-4-one (**1**), (2'*R*)-2-(2'-hydroxypropyl)-4-methoxyl-1,3-benzenediol (**2**), and 4-ethyl-3-hydroxy-6-propenyl-2*H*-pyran-2-one (**3**) were isolated from the culture broth of *Colletotrichum gloeosporioides*, an endophytic fungus derived from the mangrove *Ceriops tagal*. The structures of **1–3** were elucidated on the basis of NMR spectra and HR-ESI-MS data. Their absolute configurations were determined by comparing with the experimental and calculated ECD spectrum. Compounds **1** and **3** showed potent antibacterial activities against some of the tested microbes.

## Introduction

Endophytic fungi from plants can produce a wide range of structurally unique metabolites, and some bioactive metabolites from fungi showed antiviral [1–3], antibacterial [4, 5], and antifungal [6, 7] activities. In the past two decades, mangrove-derived microorganisms proved to be rich sources of bioactive secondary metabolites [8, 9]. The genus *Colletotrichum* is one of the most devastating groups of plant fungal pathogens [10]. The species *Colletotrichum gloeosporioides* has been isolated and investigated as not only a plant pathogen but also an endophytic fungus for the production of new bioactive secondary metabolites. Many bioactive secondary metabolites produced by *Colletotrichum* species have been reported such as aspergillomarmisin A and B, colletotric acid, selfinhibitors of conidial

germination, phytotoxins, gloeosporone, and so on [11, 12]. In the course of our searching for the new bioactive secondary metabolites from mangrove-derived endophytic fungus of Hainan island, China, three new polyketides, (2*S*)-2,3-dihydro-5,6-dihydroxy-2-methyl-4*H*-1-benzopyran-4-one (**1**), (2'*R*)-2-(2'-hydroxypropyl)-4-methoxyl-1,3-benzenediol (**2**), and 4-ethyl-3-hydroxy-6-propenyl-2*H*-pyran-2-one (**3**) were isolated from the fungus *C. gloeosporioides*, which collected from the mangrove *Ceriops tagal* in Dong Zhai port, Hainan Province. In this paper, we describe the isolation, structure elucidation, and antibacterial activities of these new compounds (Fig. 1).

## Results and discussion

Compound **1** was obtained as colorless crystals with the molecular formula C<sub>10</sub>H<sub>10</sub>O<sub>4</sub> based on the HR-ESI-MS at *m/z* 195.0647 [M + H]<sup>+</sup> (calcd. for C<sub>10</sub>H<sub>11</sub>O<sub>4</sub><sup>+</sup>, 195.0652). In the <sup>1</sup>H NMR spectrum (Table 1), two doublets protons at δ<sub>H</sub> 7.08 (d, *J* = 8.9 Hz) and 6.43 (d, *J* = 8.9 Hz) indicated the presence of an 1,2,3,4-tetrasubstituted benzene system. One hydrogenbonded hydroxy group at δ<sub>H</sub> 10.96 (s), one oxygenated methine proton signal at δ<sub>H</sub> 4.64 (qt, *J* = 6.3, 4.0 Hz), two methylene protons at δ<sub>H</sub> 2.78 (dd, *J* = 17.2, 4.0 Hz) and 2.75 (dd, *J* = 17.2, 4.0 Hz), and one methyl group at δ<sub>H</sub> 1.56 (d, *J* = 6.3 Hz) were also observed. The <sup>13</sup>C and DEPT NMR spectra of **1** displayed 10 carbons, comprising one methyl, one methylene, three methine, and five quaternary carbons with a carbonyl (δ<sub>C</sub> 197.7), which indicated a

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✉ Guang-Ying Chen  
chgying123@163.com

- <sup>1</sup> Key Laboratory of Tropical Medicinal Resource Chemistry of Ministry of Education, 571158 Haikou, People's Republic of China
- <sup>2</sup> Key Laboratory of Tropical Medicinal Plant Chemistry of Hainan Province, College of Chemistry and Chemical Engineering, Hainan Normal University, 571158 Haikou, People's Republic of China

benzoannulated  $\gamma$ -pyrone moiety. These  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (Table 1) of **1** were similar to 2,3-dihydro-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one [13]. The obvious difference was the absence of one aromatic proton signal at  $\delta_{\text{H}}$  6.48 (dd,  $J = 8.3, 0.7$  Hz) in 2,3-dihydro-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one in the  $^1\text{H}$  NMR spectrum. The corresponding carbon of **1** appeared in downfield region ( $\delta_{\text{C}}$  136.5) indicated the proton in the known compound was substituted by a hydroxyl group in **1**. The carbon was assigned to C-6 by the HMBC with H-7 (Fig. 2). Two coupling aromatic protons were assigned to C-7 and C-8 according to the HMBC of H-7 to C-5, C-6, and C-8a as well as H-8 to C-4a and C-6. Thus, the planar structure of **1** was established as 2,3-dihydro-5,6-dihydroxy-2-methyl-4*H*-1-benzopyran-4-one. The absolute configuration of **1** was determined by electronic circular dichroism (ECD) quantum chemical calculations using Gaussian 09. The ECD calculations for the two configurations were performed by TDDFT/ECD method at B3LYP/6-311 level after optimization of each possible isomers of **1**. And then the calculated ECD spectra of **1** were generated. The experimental ECD spectrum of **1** exhibited a strong negative CEs at 210.0 nm, a strong positive CEs at 274.7 nm and a weak negative CEs from 342.3 nm to 424.9 nm which in good agreement with the calculated ECD spectrum for (2*S*) con-

figuration (Fig. 3). Finally, the structure of **1** was elucidated as (2*S*)-2,3-dihydro-5,6-dihydroxy-2-methyl-4*H*-1-benzopyran-4-one.

Compound **2** was obtained as a brown oil with the molecular formula  $\text{C}_{10}\text{H}_{14}\text{O}_4$ , as determined by HR-ESI-MS at  $m/z$  221.0792  $[\text{M} + \text{Na}]^+$  (calcd. for  $\text{C}_{10}\text{H}_{14}\text{O}_4\text{Na}^+$ , 221.0784). The  $^1\text{H}$  NMR spectrum exhibited two aromatic protons [ $\delta_{\text{H}}$  6.75 (1 H, d,  $J = 8.9$  Hz, H-5),  $\delta_{\text{H}}$  7.04 (1 H, d,  $J = 8.9$  Hz, H-6)], six methyl protons [ $\delta_{\text{H}}$  1.49 (3 H, d,  $J = 6.2$  Hz, H-3'),  $\delta_{\text{H}}$  3.85 (3 H, s, H-7)], two methylene protons [ $\delta_{\text{H}}$  2.59 (1 H, dd,  $J = 16.7, 11.6$  Hz, H-1'a),  $\delta_{\text{H}}$  3.13 (1 H, dd,  $J = 16.7, 2.8$  Hz, H-1'b)], and one methine proton [ $\delta_{\text{H}}$  4.51 (1 H, qt,  $J = 6.2, 2.8$  Hz, H-2')]. The  $^{13}\text{C}$  NMR spectrum assisted by DEPT of **2** displayed 10 carbons, including two methyl groups ( $\delta_{\text{C}}$  20.7 and 56.4), one methylene ( $\delta_{\text{C}}$  29.5), three methines ( $\delta_{\text{C}}$  74.3, 111.3 and 121.4), and four quaternary carbons ( $\delta_{\text{C}}$  128.3, 145.7, 155.1 and 163.7). Two symmetric doublets of  $^1\text{H}$  NMR in the downfield region indicated a 1,2,3,4-tetrasubstituted aromatic ring. The methoxyl group ( $\delta_{\text{H}}$  3.85,  $\delta_{\text{C}}$  56.3) connected to C-4 was supported by the HMBC (Fig. 2) from H-7 to C-4 and NOE correlation of H-7 with H-5. The COSY correlations of H-1' with H-2', and H-2' with H-3', and the HMBC from H-1' and H-3' to C-2' indicated the presence the fragment of the C-1'-C-2'-C-3'. The HMBC from H-1' to C-2 and C-3 indicated the C-1' was connected with C-2. Thus, the planar structure of **2** has been established as (2'*R*)-2-(2'-hydroxypropyl)-4-methoxyl-1,3-benzenediol. In order to determine the absolute configuration, the ECD calculations for the two configurations of 2'*S* and 2'*R* were performed by the method as used in compound **1**. The experimental ECD spectrum of **2** exhibited two strong negative CEs at 201.2

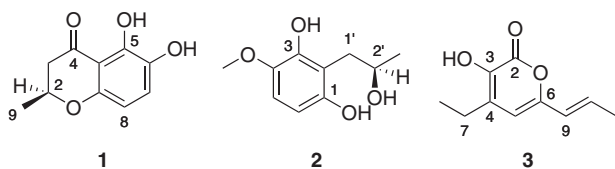


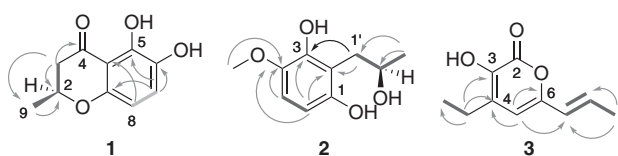
Fig. 1 Chemical structures of compounds 1–3

Table 1  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of compounds **1** and **2** in  $\text{CDCl}_3$  and **3** in  $\text{CD}_3\text{OD}$

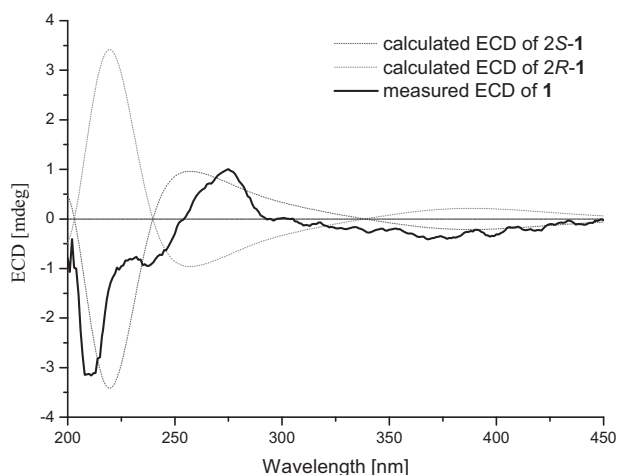
No.	Compound 1.		No.	Compound 2		No.	Compound 3	
	$\delta_{\text{H}}^{\text{a}}$ (mult, $J$ in Hz)	$\delta_{\text{C}}^{\text{b}}$ , type		$\delta_{\text{H}}^{\text{a}}$ (mult, $J$ in Hz)	$\delta_{\text{C}}^{\text{b}}$ , type		$\delta_{\text{H}}^{\text{a}}$ (mult, $J$ in Hz)	$\delta_{\text{C}}^{\text{b}}$ , type
2	4.64, qt (6.3, 4.0)	75.1, CH	1		163.7, C	2		166.5, C
3	2.78, dd (17.2, 4.0)	44.2, $\text{CH}_2$	2		128.3, C	3		166.7, C
	2.75, dd (17.2, 4.0)		3		145.7, C	4		104.9, C
4		197.7, C	4		155.1, C	5	5.96, s	99.8, CH
4a		107.8, C	5	6.75, d (8.9)	111.3, CH	6		156.8, C
5		154.6, C	6	7.04, d (8.9)	121.4, CH	7	2.41, d (7.4)	16.1, $\text{CH}_2$
6		136.5, C	7	3.85, s	56.4, $\text{CH}_3$	8	1.04, t (7.4)	11.5, $\text{CH}_3$
7	7.08, d (8.9)	124.3, CH	1'	3.13, dd (16.7, 2.8)	29.5, $\text{CH}_2$	9	6.06, dd (15.5, 1.6)	122.7, CH
8	6.43, d (8.9)	108.5, CH	2'	4.51, qt (6.2, 2.8)	74.3, CH	10	6.62, dq (15.5, 6.9)	133.2, CH
8a		146.9, C	3'	1.49, d (6.2)	20.7, $\text{CH}_3$	11	1.90, dd (6.9, 1.6)	17.0, $\text{CH}_3$
9	1.56, d (6.3)	20.9, $\text{CH}_3$						
5-OH	10.96, s							

<sup>a</sup>Measured at 400 MHz

<sup>b</sup>Measured at 100 MHz



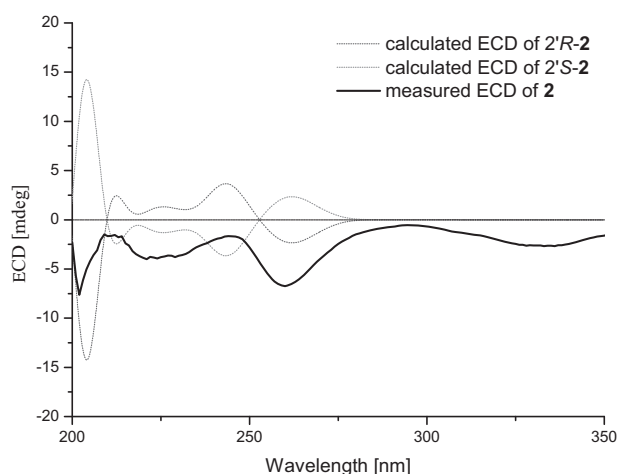
**Fig. 2** Key COSY (bold lines) and HMBC (arrows) correlations of **1–3**



**Fig. 3** Measured ECD spectrum of **1** in MeOH compared with the Boltzmann-weighted B3LYP/6–311 g (d, p) spectra calculated for the solution conformers of (2S)-**1** and (2R)-**1** in MeOH

nm and 260.0 nm which in good agreement with the calculated ECD spectrum for (2R) configuration (Fig. 4). Finally, the structure of compound **2** was elucidated as (2R)-2-(2'-hydroxypropyl)-4-methoxy-1,3-benzenediol.

Compound **3** was obtained as a white powder with the molecular formula  $C_{10}H_{12}O_3$ , as determined by HR-ESI-MS at  $m/z$  181.0856  $[M + H]^+$  (calcd. for  $C_{10}H_{13}O_3^+$ , 181.0859). The  $^1H$  NMR spectrum of **3** exhibited two methyl signals  $\delta_H$  1.04 (3 H, t,  $J = 7.4$  Hz, H-8) and 1.90 (3 H, dd,  $J = 6.9, 1.6$  Hz, H-11), one methylene signal [ $\delta_H$  2.41 (2 H, d,  $J = 7.4$  Hz, H-7)] and three methine protons  $\delta_H$  5.96 (1 H, s, H-5), 6.06 (1 H, dd,  $J = 15.5, 1.6$  Hz, H-9), and 6.62 (1 H, dq,  $J = 15.5, 6.9$  Hz, H-10). The  $^{13}C$  NMR spectrum assisted by DEPT displayed ten carbons, comprising two methyl groups ( $\delta_C$  11.5 and 17.0), one methylene ( $\delta_C$  16.1), three methines ( $\delta_C$  99.8, 122.7, and 133.2), and four quaternary carbons ( $\delta_C$  104.9, 156.8, 166.5, and 166.7). The COSY correlations of H-9 with H-10 and H-10 with H-11 indicated the presence of the propenyl moiety. The double bond configuration of the propenyl moiety was proved to be a “trans” one for the high coupling constant ( $^3J = 15.5$  Hz). The COSY correlation of H-7 with H-8, suggested an ethyl moiety. The rest of four olefin carbons and a carbonyl ( $\delta_C$  166.5) indicated a pyrone moiety, and these were confirmed by the HMBC of H-5 to C-4 and C-6 (Fig. 2). The ethyl moiety was connected to C-4 according to the HMBC from



**Fig. 4** Measured ECD spectrum of **2** in MeOH compared with the Boltzmann-weighted B3LYP/6–311 g (d, p) spectra calculated for the solution conformers of (2'R)-**2** and (2'S)-**2** in MeOH

H-7 to C-4 and C-3. And the propenyl moiety was connected to C-6 based on the HMBC from H-5 to C-4, C-6, and C-9. Finally, the structure of **3** was established as 4-ethyl-3-hydroxy-6-propenyl-2H-pyran-2-one.

The antibacterial activity of **1–3** was evaluated against five pathogenic bacteria of *Micrococcus tetragenus*, *Staphylococcus aureus*, *Streptomyces albus*, *Bacillus cereus*, and *Bacillus subtilis*. Compound **1** showed antimicrobial activity against *B. cereus* with the MIC value of  $12.5 \mu\text{g ml}^{-1}$ . Compound **3** showed antimicrobial activities against *B. subtilis*, *S. aureus*, and *S. albus* with the same MICs value of  $12.5 \mu\text{g ml}^{-1}$  (Table 2).

## Methods

### General experimental procedures

The NMR spectra were taken on a Bruker Avance 400 MHz spectrometer with tetramethylsilane as internal standard. HR-ESI-MS were acquired on Bruker APEX 7.0 TESLA FT-MS. IR spectra were recorded on a Fourier transformation infra-red spectrometer coupled with infra-red microscope (Thermo Nicolet). Optical rotation was measured on a SEPA 300 polarimeter (Horiba, Japan). UV spectra were recorded on a Shimadzu 2401 A spectrophotometer (Shimadzu, Japan) equipped with a 1-cm path-length cell. ECD spectra were recorded on a JASCO spectropolarimeter, model J-815. Column chromatography was carried out using Sephadex LH-20 (Amersham Pharmacia, Sweden) and silica gel (200–300 mesh, Qingdao Marine Chemical Factory, Qingdao, People's Republic of China). Preparative HPLC was conducted using an Agilent 1260 with the ODS column was an Agilent Zorbax SB C18 column ( $5 \mu\text{m}$ ,  $9.4 \times 150$  mm, America). Analytical thin

**Table 2** Antimicrobial activity of compounds **1–3**

Compounds	MIC ( $\mu\text{g ml}^{-1}$ )				
	<i>M. tetragenus</i>	<i>B. cereus</i>	<i>B. subtilis</i>	<i>S. aureus</i>	<i>S. albus</i>
<b>1</b>	>25	12.5	25	25	>25
<b>2</b>	>25	25	25	25	>25
<b>3</b>	>25	25	12.5	12.5	12.5
Ciprofloxacin <sup>a</sup>	6.15	5.60	0.20	1.50	6.15

<sup>a</sup>Ciprofloxacin was used as a positive control

layer chromatography (TLC) was performed with GF254 plates (Qingdao Marine Chemical Factory).

## Fungal material

*C. gloeosporioides* was isolated from the mangrove *Ceriops tagal* collected in Dong Zhai Port, Hainan Province, P. R. China. Fungus identification was carried out using a molecular biological protocol as reported, and the sequence data derived from the fungal strain has been submitted and deposited in the GenBank database under accession number MF508974. BLAST Search result showed that the sequence was the most similar (99%) to the sequence of *C. gloeosporioides* (compared to Accession No. AJ301986.1). The strain is preserved at the Key Laboratory of Tropical Medicinal Plant Chemistry of Ministry of Education.

## Extraction and isolation

### Fermentation, extraction, and isolation

For chemical investigations, the fungal strain was static cultured on the rice medium at room temperature in 1000 ml-Erlenmeyer flasks containing 50 ml rice and 50 ml seawater. After 30 days of cultivation, cultures from 200 flasks were harvested. The culture broth was filtered, and the filtrate was extracted three times with EtOAc. The EtOAc layer was concentrated under reduced pressure to give a crude extract (120 g). The extract was subjected to CC over SiO<sub>2</sub> eluted with different solvents of increasing polarity (from petroleum ether (PE) to MeOH) to yield 17 fractions (Frs. 1–17) on the basis of TLC analysis. Fr. 4 (PE–EtOAc, 5: 1, 1.5 g) was further purified by Sephadex LH-20 (CHCl<sub>3</sub>–MeOH, 1: 1) and one of the sub-fractions was purified by preparative HPLC (Acetonitrile–H<sub>2</sub>O, 39:61, 2 ml min<sup>-1</sup>) to afford compound **1** [retention time(Rt) = 13 min, 17 mg]. Fr. 6 (PE - EtOAc, 5:1, 4.5 g) was further purified by CC (PE–EtOAc, 7: 1) to yield 7 fractions(Frs. 6A–6G). Fr. 6D was further purified by Sephadex LH-20 (CHCl<sub>3</sub>–MeOH, 1: 1) and one of the sub-fractions was purified by preparative HPLC (Acetonitrile–H<sub>2</sub>O, 50:50, 2 ml min<sup>-1</sup>) to afford compound **3** (Rt = 19 min, 10 mg). Fr. 15 (EtOAc, 100%, 8 g) subjected to CC over SiO<sub>2</sub> eluted

with different solvents of increasing polarity (from CHCl<sub>3</sub>–MeOH, 50: 1 to MeOH) to yield 18 fractions (Frs. 15A–15Q) on the basis of TLC analysis. The Fr. 15B was further purified by CC (PE–EtOAc, 5:1), one of the sub-fractions was purified by preparative HPLC (Acetonitrile–H<sub>2</sub>O, 25:75, 2 ml min<sup>-1</sup>) to afford compound **2** (Rt = 16 min, 9 mg).

### (2S)-2,3-dihydro-5,6-dihydroxy-2-methyl-4H-1-benzopyran-4-one (**1**)

Colorless crystals.  $[\alpha]_D^{25}$  –0.01 (c 0.1, MeOH). UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 207 (1.81), 240 (0.71), 275 (0.90), and 380 (0.30) nm. IR (KBr)  $\nu_{\text{max}}$ : 3854, 3749, 3430, 3924, 1647, 1483, 1371, 1221, 1054, and 751 cm<sup>-1</sup>. CD (c = 0.001, MeOH)  $\lambda_{\text{max}}$  ( $\Delta\epsilon$ ): 211 (–3.2), 237 (–0.95), and 275 (+1.00). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) and <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): see Table 1. HR-ESI-MS:  $m/z$  195.0647 [M+H]<sup>+</sup> (calcd. for C<sub>10</sub>H<sub>11</sub>O<sub>4</sub><sup>+</sup>, 195.0652).

### (2'R)-4-methoxyl-2-(2'-hydroxypropyl)-1,3-benzenediol (**2**)

brown oil.  $[\alpha]_D^{25}$  –0.09 (c 0.09, MeOH). UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 200 (2.28) and 335 (0.25) nm. IR (KBr)  $\nu_{\text{max}}$ : 3421, 2930, 2366, 1709, 1591, 1495, 1451, 1384, 1249, 1204, 1125, and 1076 cm<sup>-1</sup>. CD (c = 0.001, MeOH)  $\lambda_{\text{max}}$  ( $\Delta\epsilon$ ): 202 (–7.6), 221 (–4.0), 260 (–6.7), and 337 (–2.6). <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>) and <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): see Table 1. HR-ESI-MS:  $m/z$  221.0792 [M+Na]<sup>+</sup> (calcd. for C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>Na<sup>+</sup>, 221.0784).

### 4-ethyl-3-hydroxy-6-propenyl-2H-pyran-2-one (**3**)

white powder. IR (KBr)  $\nu_{\text{max}}$ : 3856, 3750, 3434, 2930, 2359, 1658, 1566, 1406, 1126, and 711 cm<sup>-1</sup>. <sup>1</sup>H (400 MHz, CD<sub>3</sub>OD) and <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD): see Table 1. HR-ESI-MS:  $m/z$  181.0856 [M+H]<sup>+</sup> (calcd. for C<sub>10</sub>H<sub>13</sub>O<sub>3</sub><sup>+</sup>, 181.0859).

## Computational methods

Conformational searches for compounds **1** and **2** were performed via molecular mechanics using the MM +

method in HyperChem 8.0 software. The conformers were further optimized at B3LYP/6-31+g (d, p) level via Gaussian 09 software in MeOH using the CPCM polarizable conductor calculation model. The theoretical calculation of ECD was conducted in MeOH using time-dependent density functional theory (TD-DFT) at the B3LYP/6-311+g (d, p) level for all conformers of compounds in Gaussian09 software package [14]. Rotatory strengths for a total of 80 excited states were calculated. The calculated ECD spectra were generated using the program SpecDis 1.71 [15] with a half-bandwidth of 0.16 eV according to the Boltzmann-calculated distribution of each conformer.

### Antibacterial activity assay

The antibacterial activities were evaluated against five different bacteria (*Micrococcus tetragenus* ATCC35098, *S. aureus* ATCC25923, *Staphylococcus albus* ATCC 8799, *B. cereus* ATCC 14579, and *B. subtilis* ATCC6633.) in 96-well microplates as described by Correa et al. [16]. Ciprofloxacin was used as a positive control. Each assay was conducted in triplicate.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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