

Article

Alertoxins with Quorum Sensing Inhibitory Activities from the Marine-Derived Fungus *Cladosporium* sp. KFD33

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Abstract: Five new perylenequinone derivatives, alertoxins VIII-XII (1-5), as well as one known compound cladosporol I (6), were isolated from the fermentation broth of *Cladosporium* sp. KFD33 from a blood cockle from Haikou Bay, China. Their structures were determined based on spectroscopic methods and ECD spectra analysis along with quantum ECD calculations. Compounds 1-6 exhibited quorum sensing inhibitory activities against *Chromobacterium violaceum* CV026 with MIC values of 30, 30, 20, 30, 20 and 30 μ g/well, respectively.

Keywords: *Cladosporium* sp.; alertoxins; quorum sensing inhibitory activity

1. Introduction

The unremitting discovery of antibiotics showed a promising prospect for the bacterial infections, but also resulted in the serious resistance of antibiotics. What's worse, bacteria have evolved a variety of resistance mechanisms [1-2]. Quorum sensing (QS) controls the production of virulence factors in many pathogenic bacteria in a population density dependent manner through intercellular communication mechanism [3]. Thus, the search for efficient quorum sensing inhibitors (QSIs) is supposed to be an effective method to solve problems of bacterial infection and antibiotic resistance. Based on this, a screening system was established to search for quorum-sensing inhibitors [4]. Due to the special environmental conditions, marine-derived fungi, as a rich source of various compounds with complex structures and excellent activities, have attracted more and more attention [5]. Our previous research on new bioactive metabolites from marine-derived fungi has led to the isolation and identification of a series of new QSIs, such as aculene E and penicitor B, aculene C, aculene D, aspergillumarins A-B [6], asperochrin D, asperochrin F, (3R,4R)-4,7-dihydroxymellein, asperochrin A and asteltoxin [7]. As our ongoing research, the fungus *Cladosporium* sp. KFD33 was isolated from a blood cockle from Haikou Bay, China. The EtOAc extract of the fermentation broth of this fungus showed obvious QS inhibitory activity against *Chromobacterium violaceum* CV026. Subsequent chemical investigation on the EtOAc extract of the fermentation broth had led to the isolation of five new compounds, named alertoxins VIII-XII (1-5), as well as a known cladosporol I (6) [8]. All the new compounds showed obvious QS inhibitory activities. Herein, the isolation, structural elucidation, and quorum sensing inhibitory activity of compounds 1-6 are described.

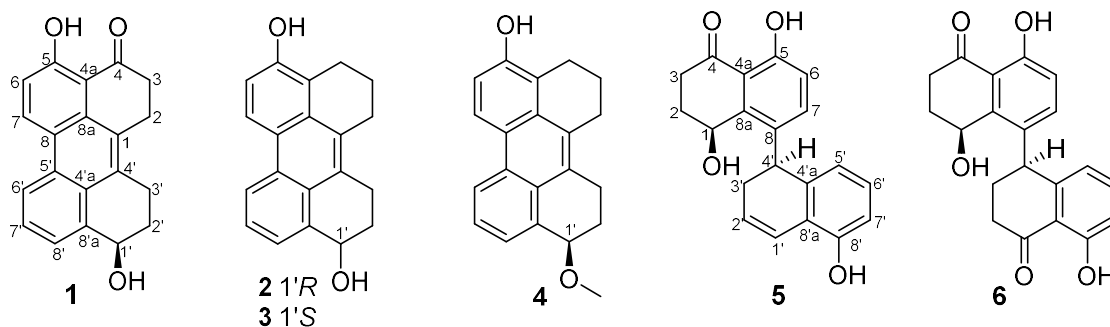


Figure 1. The chemical structures of compounds 1-6.

2. Results and discussions

Compound **1** was obtained as a dark yellow powder, and its molecular formula was determined as $C_{20}H_{16}O_3$ on the basis of HRESIMS data, indicating 13 degrees of unsaturation. The ^{13}C -NMR and HSQC spectra showed 20 carbon signals assigned to four methylenes, 14 aromatic carbons with five protonated, one oxygenated sp^3 methine, and a conjugated ketone carbonyl. Analysis of its 1H and ^{13}C NMR data (Table 1 and 2) revealed the presence of a 1,2,3-trisubstituted and a 1,2,3,4-tetrasubstituted benzene rings. The COSY correlations of H_{2-3}/H_2-2 and $H-6/H-7$ along with the HMBC correlations from H_2-3 (δ_H 2.84) to C-4 (δ_C 204.8), C-4a (δ_C 110.7), C-1 (δ_C 125.2) and C-2 (δ_C 23.6), from H_2-2 (δ_H 3.22) to C-8a (δ_C 131.0) and C-1, from $H-6$ (δ_H 7.13) to C-8 (δ_C 121.3) and C-4a, and from $H-7$ (δ_H 8.92) to C-5 (δ_C 161.8) and C-8a, suggested the presence of a substituted 1-tetralone moiety. The observed COSY correlations of $H-1'/H_2-2'/H_2-3'$ as well as the HMBC correlations from $H-1'$ (δ_H 4.80) to C-8'a (δ_C 139.7) and C-4'a (δ_C 126.1), from H_2-3' (δ_H 2.96, 3.15) to C-4' (δ_C 132.9), from H_2-2' (δ_H 1.84, 2.06) to C-4', from $H-6'$ (δ_H 8.52) to C-8' (δ_C 123.8) and C-4'a, and from $H-7'$ (δ_H 7.52) to C-5' (δ_C 128.7) and C-4'a revealed the presence of a substituted 1-butanol moiety. Furthermore, the observed HMBC correlations from H_2-2 to C-4' and from $H-3'$ to C-1 suggested that there is a C-1/C-4' linkage. The observed HMBC correlations from $H-7$ to C-5' and from $H-6'$ to C-8 suggested that there is a C-8/C-5' linkage. The above data revealed that compound **1** was structurally similar to altertoxin VII [9], except for the absence of a hydroxyl group located at C-7' (δ_C 126.2). The ECD curve of **1** showed negative Cotton effects (CEs) around 225 and 260 nm and positive one around 280 nm, which is very similar to that of altertoxin VII [9], suggesting their same absolute configuration, i.e. 1'R.

Compounds **2** and **3** were obtained as yellow powder, exhibiting two totally overlapped peaks over Rp-18 column and two independent peaks with a peak area ratio of 1:2 over a chiral column (Supporting information), suggesting that they are pair of enantiomers, which were different to each other at the absolute configuration in C-1'. Their formulas were determined as $C_{20}H_{18}O_2$ on the basis of HRESIMS, indicating 12 degrees of unsaturation. Analysis of the 1D NMR data of **2** and **3** revealed that their planar structures are similar to that of **1**, except that the C-4 carbonyl in **1** was replaced by a methylene in **2** and **3**. This deduction was further confirmed by COSY correlations of $H_2-2/H_2-3/H_2-4$. In order to determine the absolute configuration of the stereocenter C-1' of compounds **2** and **3**, the ECD spectra of (*R*)-**2** and (*S*)-**2** were calculated and compared with the experimental ECD spectra of **2** and **3**. As can be seen in Figure 3, the calculated ECD spectrum for (*R*)-**2** and (*S*)-**2** matched well with the experimental ECD spectra of **2** and **3**, respectively, indicating that the absolute configuration of C-1' in compound **2** is *R* and in compound **3** is *S*.

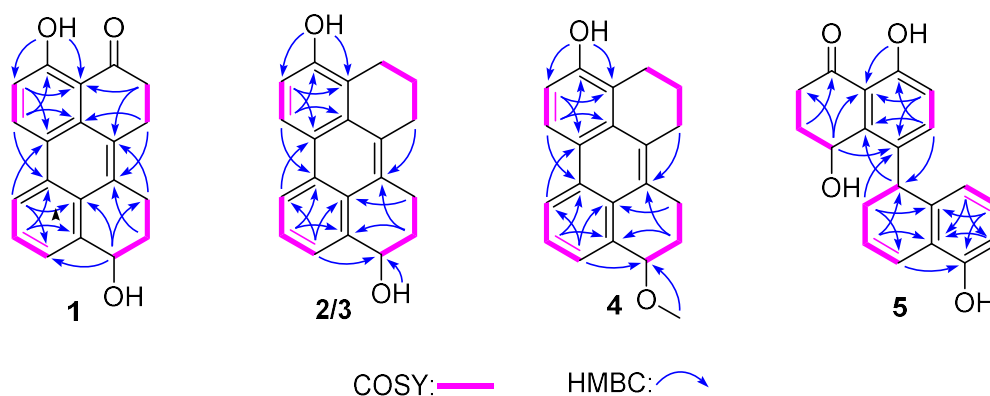


Figure 2. Key COSY and HMBC correlations of compounds 1-5.

The molecular formula of compound **4** was determined as $C_{21}H_{20}O_2$ based on HRESIMS, indicating 12 degrees of unsaturation. The ^{13}C -NMR data of **4** are similar to those of **2** and **3** except for the presence of an methoxy carbon (δ_c 55.2) in **4**. In the HMBC spectrum, correlation from the protons of this carbon to C-1' (δ_c 76.8) was observed, indicating that the OH-1' in **2** or **3** was methylated in **4**. The remaining substructure of **4** was determined to be the same as those of **2** and **3** by detailed analysis of its 2D NMR data (Figure 2). The absolute configuration of the stereocenter C-1' in **4** was determined to be the same as that of **2** by their similar ECD curves (Figure 3) and same sign of optical rotation values.

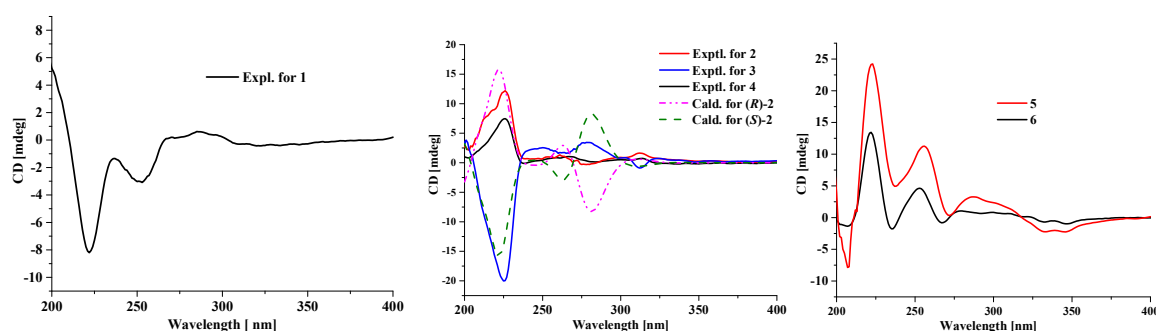


Figure 3. Experimental ECD spectra for compounds 1-6 and calculated ECD spectra for (R)-**2** and (S)-**2**.

Compound **5** was obtained as a yellow powder, and its formula was determined as $C_{20}H_{18}O_4$ on the basis of HRESIMS data, indicating 12 degrees of unsaturation. Comprehensive analysis of the NMR data of **5** revealed that its structure is very similar to that of cladosporol I (**6**), except for the absence of the C-1' (δ_c 121.9) carbonyl and the presence of a double bond which was located at C-1' and C-2' (δ_c 125.9) in **5** as deduced from the COSY correlations of H-1'/H-2'/H-3'/H-4' as well as the HMBC correlations from H₂-3' (δ_H 2.29, 2.47) to C-1' and C-4'a (δ_c 139.4) and from H-2' (δ_H 5.89) to C-4' (δ_c 37.5) and C-8'a (δ_c 121.2). The absolute stereochemistry of the asymmetric C-4' was estimated from the ECD spectrum. In the ECD spectrum of **5**, there was a strong splitting cotton effect centered at 216 nm, which should be originated from exciton chirality caused by interaction between two phenolic chromophores [10]. Thus, according to the exciton chirality rule, the absolute stereochemistry of C-4' was determined to be S. In addition, the absolute configuration of the C-1 (δ_c 61.3) stereocenter in cladosporol I (**6**) has been determined by comparison of the experimental ECD curve with the calculated ECD curves of the two C-1 epimers (1R, 4S)-**6** and (1S,4S)-**6** [8]. According to the results, the calculated ECD curve for (1S, 4S)-**6** showed an intense positive CE around 225 nm, which matched well with the experimental one and was absent in the calculated ECD curve for (1R, S)-**6**. Thus, the intense positive CE around 225 nm can be used to differentiate (1R, 4S)-**6** and (1S, 4S)-

6. The experimental ECD curve of **5**, with an intense positive CE around 225 nm, is very similar to that of (1*S*, 4*S*)-**6**, indicating that the absolute configuration of C-1 is *S*, same as that of **6**. All the isolated compounds were screened for quorum sensing inhibitory activity against *Chromobacterium violaceum* CV026 [6]. Compounds **1-6** showed obvious activity (Figure S34, Supporting Information) and the MIC values were finally determined to be 30, 30, 20, 30, 20 and 30 μ g/well, respectively.

Table 1. ^1H (500 MHz) data of **1-5** in DMSO.

Position	1	2/3	4	5
	δ_{H} (J in Hz)	δ_{H} (J in Hz)	δ_{H} (J in Hz)	δ_{H} (J in Hz)
1				4.81, dd, (3.2, 3.2)
2	3.22, t, (7.4)	2.84, t, (6.0)	2.92, overlap	2.01, m 2.05, m
3	2.84, t, (7.4)	1.80, overlap	1.81, m 1.92, overlap	2.36, overlap 2.97, ddd, (18.4, 13.2, 5.9)
4		2.78, overlap 2.86, overlap	2.78, m 2.90, overlap	
6	7.13, d, (9.1)	7.04, d, (9.0)	7.11, d, (9.0)	6.76, d, (8.8)
7	8.92, d, (9.1)	8.32, d, (9.0)	8.40, d, (9.0)	7.31, d, (8.8)
1'	4.80, dd, (3.6, 8.4)	4.74, dd, (8.3, 3.7)	4.47, m	6.73, overlap
2'	1.84, dtd, (13.0, 8.7, 4.7) 2.06, m	1.78, overlap 2.00, m	1.97, overlap 2.15, m	5.89, overlap
3'	2.96, ddd, (16.7, 9.0, 4.8) 3.15, ddd, (16.7, 7.0, 4.8)	2.82, overlap 3.02, m	2.89, overlap 3.03, m	2.29, ddd, (16.9, 6.3, 6.3) 2.47, m
4'				4.34, dd, (12.6, 7.0)
5'				5.89, overlap
6'	8.52, d, (8.3)	8.39, d, (8.3)	8.53, d, (8.4)	6.74, overlap
7'	7.52, dd, (7.1, 8.3)	7.37, dd (7.1, 8.3)	7.43, dd, (7.0, 8.4)	6.55, d, (8.0)
8'	7.58, d, (7.1)	7.45, d, (7.1)	7.39, d, (7.0)	
9'			3.24, s	
5-OH	13.15, s		9.52, s	12.57, s
1'-OH	5.40, s	5.26, s		9.39, s

Table 2. ^{13}C NMR (125 MHz) data of **1-5** in DMSO.

Position	1	2/3	4	5
1	125.2, C	128.7, C	129.3, C	61.3, CH
2	23.6, CH ₂	27.1, CH ₂	27.0, CH ₂	29.8, CH ₂
3	36.3, CH ₂	21.9, CH ₂	21.8, CH ₂	32.1, CH ₂
4	204.8, C	23.4, CH ₂	23.3, CH ₂	206.3, C
4a	110.7, C	119.0, C	118.9, C	115.1, C
5	161.8, C	152.1, C	152.2, C	160.5, C
6	117.0, CH	115.5, CH	115.5, CH	117.2, CH
7	133.4, CH	121.5, CH	121.5, CH	137.3, CH
8	121.3, C	122.2, C	122.1, C	132.9, C
8a	131.0, C	129.7, C	129.6, C	142.7, C
1'	67.2, CH	67.6, CH	76.8, CH	121.9, CH
2'	31.2, CH ₂	31.5, CH ₂	27.2, CH ₂	125.9, CH
3'	24.0, CH ₂	23.8, CH ₂	22.5, CH ₂	30.3, CH ₂
4'	132.9, C	127.9, C	127.5, C	37.5, CH
4'a	126.1, C	125.9, C	126.0, C	139.4, C

5'	128.7, C	129.3, C	129.6, C	117.9, CH
6'	121.4, CH	121.2, CH	122.2, CH	127.7, CH
7'	126.2, CH	125.1, CH	124.6, CH	113.7, CH
8'	123.8, CH	123.1, CH	125.2, CH	152.6, C
8'a	139.7, C	139.2, C	134.1, C	121.2, C
9'			55.2, CH ₃	

3. Experimental

3.1. General experimental procedures

The NMR spectra were recorded with a Bruker AV-500 spectrometer (Bruker, Bremen, Germany) using TMS as an internal standard. The mass spectrometric (HRESIMS) data were acquired using an API QSTAR Pulsar mass spectrometer (Bruker, Bremen, Germany). Optical rotations were measured with a JASCO P-1020 digital polarimeter. The infrared spectra were recorded on a Shimadzu UV2550 spectrophotometer (Shimadzu, Kyoto, Japan). Silica gel (60–80 and 200–300 mesh; Qingdao Haiyang Chemical Co. Ltd., Qingdao, China) and Rp-C18 (20–45 µm; Fuji Silysia Chemical Ltd., Durham, NC, USA) were used for column chromatography. Semipreparative high-performance liquid chromatography (HPLC) equipped with octadecyl silane (ODS) column (Cosmosil ODS-A, 10×250 nm, 5 µm, 4 mL/min) and chiral column (CHIRALPAK IC, 4.6×250 nm, 5 µm, 1 mL/min) were used to isolate compounds. The solvents used to the extraction or isolation of the columns, such as ethyl acetate, methanol, chloroform and methanol, were of analytical pure (Concord Technology Co. Ltd., Tianjin, China). The solvents used to the preparative HPLC, such as methanol, acetonitrile, hexane and ethanol were of chromatographic grade (Concord Technology Co. Ltd., Tianjin, China).

3.2. Fungus material

The fungal strain *Cladosporium* sp. KFD33 with yellow mycelium was isolated from a blood cockle in the Haikou Bay, Hainan province, in China in August 2018. After grinding, the sample (1 g) was diluted to 10⁻² g/mL with sterile H₂O, 100 µL of which was spread on a PDA medium plate containing chloramphenicol as bacterial inhibitor. It was identified by its morphological characteristics and 18S rRNA gene sequences (GenBank accessing No. MN737504, Supporting Information). A reference culture of *Cladosporium* sp. KFD33 is deposited in our laboratory and which maintained at -80°C.

3.3. Culture conditions

Plugs of agar, supporting mycelial growth, were cut from solid culture medium and transferred aseptically to a 1000 mL Erlenmeyer flask, containing 300 mL liquid medium (peptone 5 g/L, yeast extract 2 g/L, glucose 20 g/L, MgSO₄ 0.5 g/L, KH₂PO₄ 2 g/L). The fungus was cultured in the medium and incubated at room temperature for thirty days.

3.4. Extraction and isolation

The whole culture broth (20 L) was harvested and filtered to yield the mycelium cake and liquid broth. The mycelium cake was extracted by tissue crusher using EtOAc for three times. The EtOAc solution was evaporated under reduced pressure. A total of 10 g EtOAc extract was obtained. The EtOAc extract was submitted to silica gel vacuum liquid chromatography using step gradient elution with PE-EtOAc (8:1, 6:1, 4:1, 2:1, 1:1, 0:1, v/v) to obtain six fractions (Frs.1–6) based on HPLC. Fr.1 (2 g) was further chromatographed on Rp-C₁₈ silica gel column eluted with MeOH-H₂O (from 10%–100%) to give three subfractions (Fr.1-1–Fr.1-3) based on HPLC. Compounds **1** (1.0 mg, *t_R* 25.9 min) and **5** (1.1 mg, *t_R* 10.0 min) and **6** (5.3 mg, *t_R* 19.6 min) were obtained from Fr.1-1 (15.0 mg) by ODS chromatography eluting with MeOH-H₂O (10%–100%) and semipreparative HPLC (40% MeOH/H₂O, containing 0.1% Formic acid, 4.0 mL·min⁻¹). Compounds **2**, **3** (2.1 mg, *t_R* 10.7 min) and **4** (1.9 mg, *t_R* 32.2 min) were obtained from Fr.1-2 (6.3 mg) by ODS chromatography eluting with MeOH-H₂O (10%–

100%) and semipreparative HPLC (65% MeOH/H₂O, containing 0.1 % Formic acid, 4.0 mL·min⁻¹). Compounds **2** (0.3 mg, *t_R* 24.6 min) and **3** (0.5 mg, *t_R* 27.2 min) were further obtained by semipreparative HPLC (99% Hexane/EtOH, 1.0 mL·min⁻¹), using a chiral column.

Altertoxin VIII (**1**): Dark yellow powder; $[\alpha]_D^{25}$ -9.0 (c 0.1, MeOH); UV (CH₃OH) λ_{max} (log ϵ): 252 (3.16) nm; 217 (2.97); ECD (CH₃OH) λ_{max} ($\Delta\epsilon$): 222 (-1.94) nm; 237 (-0.32) nm; 250 (-0.71) nm; 270 (0.05) nm; 322 (-0.10) nm; IR(KBr) ν_{max} : 3418, 2924, 2856, 1625, 1415, 1027 cm⁻¹; ¹H and ¹³C NMR spectral data, Tables 1 and 2; HRESIMS *m/z* 327.0952 ([M + Na]⁺ calcd 327.0992).

Altertoxin IX (**2**): Yellow powder; $[\alpha]_D^{25}$ +35.0 (c 0.01, MeOH); UV (CH₃OH) λ_{max} (log ϵ): 264 (3.14) nm; ECD (CH₃OH) λ_{max} ($\Delta\epsilon$): 226 (16.08) nm; 261 (1.77) nm; 278 (-0.39) nm; 312 (2.16) nm; IR(KBr) ν_{max} : 3437, 2925, 1569, 1415 cm⁻¹; ¹H and ¹³C NMR spectral data, Tables 1 and 2; HRESIMS *m/z* 313.1186 ([M + Na]⁺ calcd 313.1199).

Altertoxin X (**3**): Yellow powder; $[\alpha]_D^{25}$ -34.0 (c 0.01, MeOH); UV (CH₃OH) λ_{max} (log ϵ): 264 (3.14) nm; ECD (CH₃OH) λ_{max} ($\Delta\epsilon$): 225 (-9.23) nm; 250 (1.18) nm; 265 (1.56) nm; 276 (-0.41) nm; 312 (-0.41) nm; 324 (0.34) nm; IR(KBr) ν_{max} : 3437, 2925, 1569, 1415 cm⁻¹; ¹H and ¹³C NMR spectral data, Tables 1 and 2; HRESIMS *m/z* 313.1186 ([M + Na]⁺ calcd 313.1199).

Altertoxin XI (**4**): Yellow powder; $[\alpha]_D^{25}$ +18.0 (c 0.01, MeOH); UV (CH₃OH) λ_{max} (log ϵ): 264 (3.16) nm; ECD (CH₃OH) λ_{max} ($\Delta\epsilon$): 226 (3.44) nm; 238 (-0.05) nm; 267 (0.48) nm; 284 (0.06) nm; 314 (0.34) nm; 336 (-0.09) nm; IR (KBr) ν_{max} : 3440, 2924, 2854, 1689, 1584, 1418, 1207 cm⁻¹; ¹H and ¹³C NMR spectral data, Tables 1 and 2; HRESIMS *m/z* 327.1323 ([M + Na]⁺ calcd 327.1356).

Altertoxin XII (**5**): Yellow powder; $[\alpha]_D^{25}$ +61.0 (c 0.01, MeOH); UV (CH₃OH) λ_{max} (log ϵ): 261 (3.21) nm; ECD (CH₃OH) λ_{max} ($\Delta\epsilon$): 207 (-4.32) nm; 223 (13.32) nm; 237 (2.71) nm; 256 (6.19) nm; 272 (0.18) nm; 287 (1.80) nm; 346 (-1.24) nm; IR (KBr) ν_{max} : 2923, 2851, 1636, 1453, 1355, 1235, 807 cm⁻¹; ¹H and ¹³C NMR spectral data, Tables 1 and 2; HRESIMS *m/z* 361.0856 ([M + K]⁺ calcd 361.0837).

4. Conclusions

In conclusion, five new perylenequinone derivatives, altertoxins VIII-XII (**1-5**), as well as the known compound cladosporol I (**6**), were isolated from the marine fungi *Cladosporium* sp. KFD33, which was isolated from a blood cockle. Compounds **1-6** represent a new type of QSIs with QS inhibitory activity against *Chromobacterium violaceum* CV026 with MIC values of 30, 30, 20, 30, 20 and 30 µg/well, respectively.

Supplementary Materials: Figures S1-S31: 2D NMR, IR and HRESIMS spectra of the new compounds **1-5**, the 18S rRNA gene sequence of *Cladosporium* sp. KFD33, as well as the picture of quorum sensing inhibitory activity of compounds **1-6** against *Chromobacterium violaceum* CV026 are supplied.

Author Contributions: F. Z contributed to fungal isolation and fermentation and compounds purification. F.D. K and L.M. Z were responsible for the structural elucidation and chemical computation. Q.Y. M and Q.Y. X contributed to the bioassays. J. H. L. and H.F. D. revised the paper. Y.X. Z and L. G designed the work and revised the paper.

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Conflicts of Interest: The authors declare no conflict of interest.

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