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深海来源篮状菌 *Talaromyces indigoticus* FS688 中聚酮化合物及其细胞毒性

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摘要 对深海来源真菌 *Talaromyces indigoticus* FS688 进行化学成分研究, 从中发现了 3 个新的聚酮类化合物以及 5 个已知化合物, 其化学结构是通过综合的波谱分析得以确定, 同时其绝对构型是通过理论电子圆二色谱(ECD)计算确定. 其中, 5-甲基六氢呋喃[2,3-*b*]呋喃-2-基-乙烷-1-醇(**2**)对所测试的 4 株人体肿瘤细胞株(SF-268, MCF-7, HepG-2 和 A549)表现出显著的细胞毒活性, IC_{50} 介于 0.18～0.53 μmol/L 之间.

关键词 *Talaromyces*; 深海真菌; 聚酮; 波谱分析; 细胞毒

Polyketides from the Deep-Sea-Derived Fungus *Talaromyces indigoticus* FS688 and Their Cytotoxicites

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Abstract The chemical investigation of the deep-sea-derived fungus *Talaromyces indigoticus* FS688 led to the isolation of three new polyketides together with five known compounds. Their structures were determined by comprehensive spectroscopic analysis and the absolute configurations were evaluated by theoretical electrostatic circular chroism (ECD) calculations. Among them, 5-methylhexahydrofuro[2,3-*b*]furan-2-yl-ethan-1-ol (**2**) exhibited significant cytotoxicity against the four tested human tumor cell lines (SF-268, MCF-7, HepG-2 and A549) with the IC_{50} values in the range of 0.18～0.53 μmol/L.

Keywords *Talaromyces*; deep-sea-derived fungus; polyketide; spectroscopic analysis; cytotoxicity

1 Introduction

The genus *Talaromyces* is an important fungal genus and widely distributes in soil, plant, marine environment and several foods.[1] Initially, *Talaromyces* were identified to be the species which could produce sexual stages with *Penicillium* anamorphs. In 2011, the species formally classified in the *Penicillium* subgenus *Biverticillium* were re-classified in *Talaromyces*, of which the ascocarps look like 'basket'.[2] In general, the secondary metabolites discovered from *Talaromyces* usually construct novel frameworks and

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exhibit diverse bioactivities. Two comprehensive reviews published by Lan and Zhai *et al*.[1,3] summarized more than 300 secondary metabolites mainly belonging to polyketides, alkaloids and meroterpenoids. In the recent two years, an increased number of structurally novel and biological active compounds have been isolated from *Talaromyces*, such as the anti-microbiol nonadride derivatives talarodrides A～F[4] and the phosphatase CDC25B inhibitory meroterpenoids talaromynoids A～I.[5] Therefore, the genus *Talaromyces* is a potential fungal resource of lead compounds for drug development.

Deep-sea-derived fungi are a special group of microorganisms collected from the sediment or water at a depth over 1000 m. Because of their extreme living environment, the deep-sea-derived fungus always exhibit complex metabolic mechanisms and could produce novel secondary metabolites with diverse bioactivities, which have attracted considerable attention and become the research hotspots in recent years.[6] During the course of our search for bioactive secondary metabolites from deep-sea-derived fungi, a strain *Talaromyces indigoticus* FS688 attracted our attention because of its ability to produce thioester-containing benzoate derivatives with *α*-glucosidase inhibitory activity.[7] In this study, the strain FS688 was fermented in potato dextrose agar (PDB) culture and the chemical investigation of the extract led to the isolation of three new polyketides (**1**～**3**) as well as five known compounds (Figure 1). In the bioassays, compounds **2** and **3** exhibited potential cytotoxicity against four tested human tumor cell lines. Herein, the details of the isolation, structural identification and bioactivity are discussed.

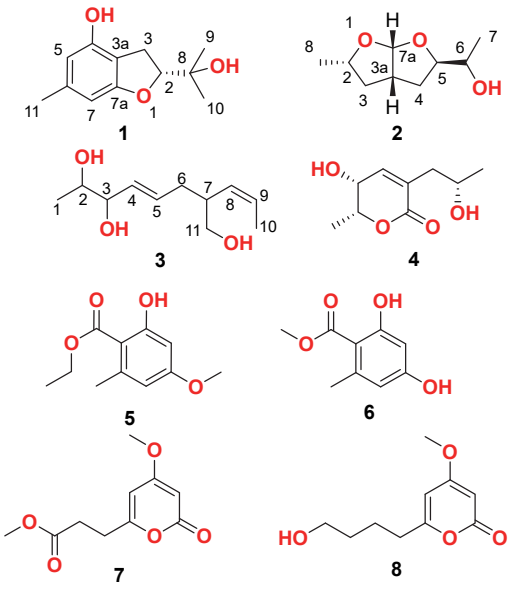

Figure 1 Chemical structures of **1**～**8**

2 Results and discussion

Compound **1** was obtained as colorless oil and the molecular formula was deduced to be $C_{12}H_{16}O_3$ through HR-ESI-MS, which gave a deprotonated molecular ion peak at *m*/*z* 207.1020 (calcd for $C_{12}H_{15}O_3$ $[M-H]^-$ 207.1027). The ^1H NMR spectrum exhibited a set of *meta*-coupled aromatic protons at δ_H 6.01/6.06 (brs), a methylene group at δ_H 2.90, an oxygenated methine group at δ_H 4.46 and three methyl groups at δ_H 1.07, 1.11 and 2.12. The ^{13}C NMR spectrum resolved 12 signals including a benzene ring, three methyl groups, a methylene group, a methine group as well as a quaternary carbon (δ_C 70.1) (Table 1). In consideration of the degrees of unsaturation, an additional ring should be existed except for the benzene ring.

The COSY (correlation spectroscopy) between H_2-3 and H-2 indicated the only independent coupling unit of C-2/C-3 in **1**, which was connected to C-3a of the benzene ring based on the HMBC (heteronuclear multiple-bond correlation) from H_2-3 to C-4, C-3a and C-7a (Figure 2). The correlations from H_3-9 and H_3-10 to C-8 and C-2 combined with the deshielded chemical shift of C-8 revealed an oxidized isoprenyl unit, while a benzofuran moiety was evaluated by the requirement of the degrees of unsaturation as well as the deshielded chemical shift of C-7a (δ_C 153.6). Finally, the substitution of C-6 with a methyl group was deduced through the correlations from H_3-11 to C-5, C-6 and C-7. Hence, the planar structure was established to be (2-hydroxypropan-2-yl)-6-methyl-2,3-dihydrobenzofuran-4-ol.

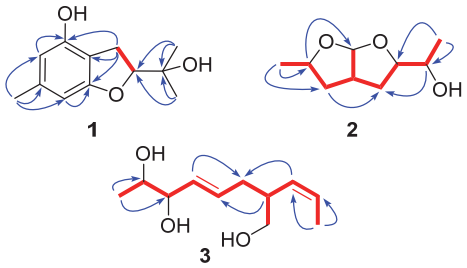

Figure 2 Key COSY (red bold) and HMBC (blue arrows) correaltions of **1**～**3**

Since there was only one chiral center in compound **1**, the absolute configuration of C-2 was determined by comparing the experimental ECD spectrum to the theoretical plots of the two possible candidates (2*S*-**1** and 2*R*-**1**) calculated at PBE1PBE/tzvp level (Figure 3). The calculated plot of 2*R*-**1** exhibited a good fit to the experimental one, thus, the absolute configuration was assigned as 2*R*.

The molecular formula of compound **2** was identified to be $C_9H_{16}O_3$ by a protonated molecular ion peak at *m*/*z* 173.1175 (calcd for $C_9H_{17}O_3$ $[M+H]^+$ 173.1172) from HR-ESI-MS. The 1D NMR data indicated the presence of two methyl groups (δ_H/δ_C 1.13/18.2 and 1.31/20.6), two methylene groups and five sp^3 hybrid methine groups, and no quaternary or unsaturated carbon were detected (Table 1). Further analysis of the COSY spectra suggested that all the carbons were correlated and formed a long independent coupling chain, which started at Me-8 and terminated at Me-9 (Figure 3). The gross structure was determined by the HMBC correlations, the ^{13}C NMR chemical shift as well as

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Table 1 1D NMR data of **1** and **2** (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR)

Position	**1**[a]		Position	**2**[b]	
	δ_H, (J in Hz)	δ_C (type)		δ_H, (J in Hz)	δ_C (type)
2	4.46 (t, J=8.9)	89.1 (CH)	2	3.96 (dt, J=10.0, 5.0)	75.2 (CH)
3	2.90 (d, J=8.9)	27.5 (CH_2)	3	1.23 (m)	39.1 (CH_2)
3a		109.6 (C)		2.22 (ddd, J=12.4, 10.0, 5.3)	
4		161.3 (C)	3a	2.91 (qd, J=8.8, 5.3)	43.6 (CH)
5	6.01 (s)	100.9 (CH)	4	1.61 (dd, J=12.4, 4.5)	30.8 (CH_2)
6		137.8 (C)		1.94 (ddd, J=12.4, 10.4, 8.8)	
7	6.06 (s)	108.1 (CH)	5	4.03～4.12 (m)	81.1 (CH)
7a		153.6 (C)	6	4.03～4.12 (m)	66.7 (CH)
8		70.1 (C)	7	1.13 (d, J=6.3)	18.2 (CH_3)
9	1.07 (s)	24.6 (CH_3)	7a	5.63 (d, J=5.3)	108.8 (CH)
10	1.11 (s)	26.1 (CH_3)	8	1.31 (d, J=6.0)	20.6 (CH_3)
11	2.12 (s)	21.3 (CH_3)			
4-OH	9.17 (s)				
8-OH	4.51 (s)				

[a] Measured in DMSO-d_6; [b] measured in chloroform-d.

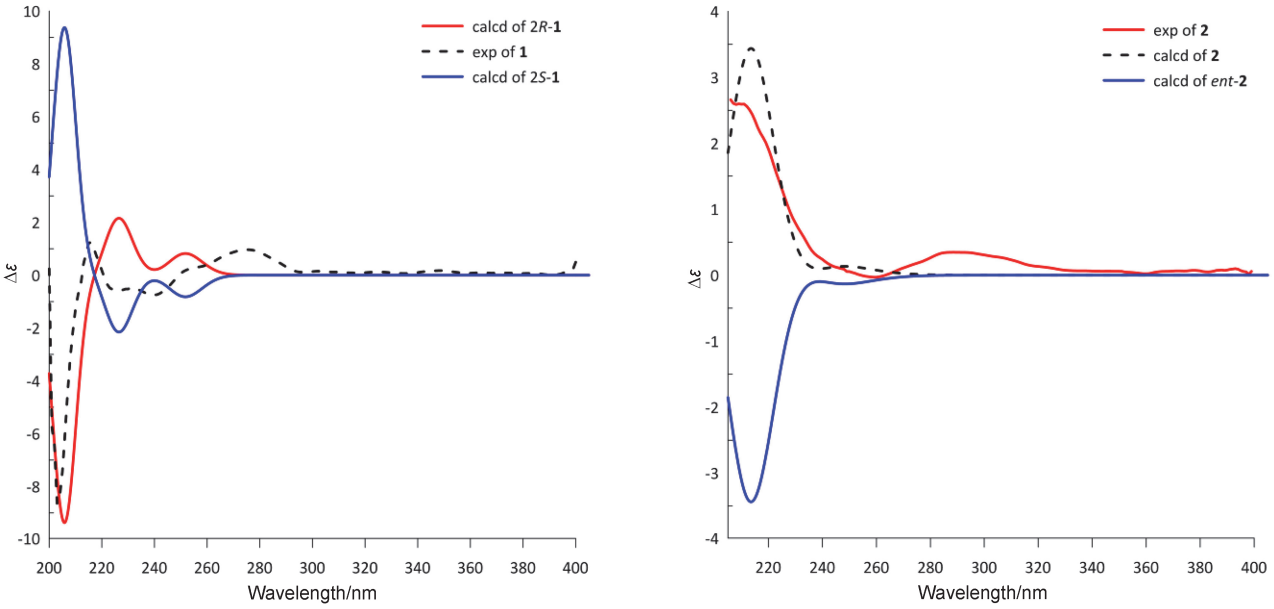

Figure 3 Calculated ECD spectra of **1**/**2** and their experimental plots

the degrees of unsaturation. Firstly, the correlations from H-2 to C-7a constructed a furan ring A and another ring should be existed according to the requirement of degrees of unsaturation. Secondly, the chemical shift of C-5 was more deshielded obviously than that of C-6, suggesting that C-5 should be cyclized with C-7a via an oxygen to form ring B. Hence, the planar structure was identified to be 5-methyl-hexahydrofuro[2,3-*b*]furan-2-yl)-ethan-1-ol.

The relative configuration was determined by the NOE (Nuclear Overhauser Effect) correlations and the H-H coupling constant (Figure 4). On one hand, the NOE cross-peaks of H-2/H-3a/H-7a combined with the small coupling constant between H-3a and H-7a (5.3 Hz) indicated the same α-orientation of them. On the other hand, the large coupling constants between H-4α and H-3a/H-5 (8.8/10.4 Hz) and the small coupling constants between H-4β and H-3a/H-5 (0/4.5 Hz) suggested the β-orientation of H-5, which was further supported by the NOE correlation between H-5 and H-3β. However, due to the less amount of the compound **2** obtained, the Mosher's reaction could not be accomplished and the configuration of C-6 was not assigned. Nevertheless, the absolute configuration could be deduced by comparing the calculated ECD spectra and the experimental plot since the Cotton effect was mainly contributed by the configurations of rings A and B. The theoretical plots of the two enantiomers (**2** and *ent*-**2**) were calculated at cam-b3lyp/def2tzvp level and the calculated ECD spectrum of **2** showed a good fit to the experimental one (Figure 3). Thus, the absolute configuration was assigned to be 2*S*,3a*S*,5*R*,7a*R*.

Compound **3** was isolated as a colorless oil with the molecular formula of $C_{11}H_{20}O_3$ ([M+Na$^+$], *m*/*z* 223.1310 calcd for 223.1305, $C_{11}H_{20}O_3Na$). The ^{1}H NMR data exhibited two doublet methyl signals at δ_H 1.11 (d, J=6.4 Hz)

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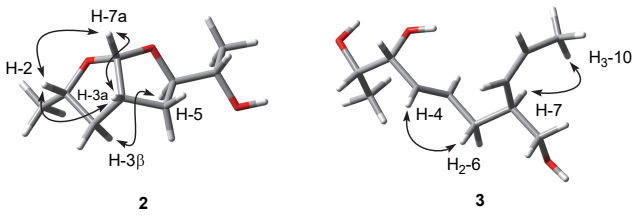

Figure 4 Key NOESY correlations of **2** and **3**

and 1.64 (d, J=6.8 Hz) as well as several sets of multiplets in the range of δ 2.00～6.00 (Table 2). The ^{13}C NMR showed 11 signals including four sp^2 hybrid carbons, three oxygenated ones and four aliphatic carbons. The planar structure was established to be (*E*)-2-((*Z*)-prop-1-en-1-yl)-oct-4-ene-1,6,7-triol by analysis of the 2D NMR spectra. The COSY correlations from H_3-1 to H_3-10 constructed a chain structural framework and the HMBC correlations from H_2-11 to C-6, C-7 and C-8 indicated a hydroxymethyl attached to C-7. The *E* configuration of Δ^4 and the *Z* configuration of Δ^8 were evaluated by the NOESY (nuclear overhauser effect spectroscopy) cross-peaks of H-4/H_2-6 and H_3-10/H-7, respectively (Figure 4). However, the absolute configuration could not be determined at the present study because the amount of compound left was not enough for further experiments.

Table 2 1D NMR data of **3** (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR)

Position	δ_H, (J in Hz)	δ_C (type)
1	1.11 (d J=6.4)	18.1 (CH_3)
2	3.76～3.86 (m)	70.5 (CH)
3	3.98 (ddd, J=10.8,7.2,3.8)	76.8 (CH)
4	5.49~5.58 (m)	129.8 (CH)
5	5.62～5.75 (m)	132.7 (CH)
6	1.98～2.09 (m)	35.1 (CH_2)
	2.17～2.27 (m)	
7	2.66～2.76 (m)	40.1 (CH)
8	5.10～5.20 (m)	131.3 (CH)
9	5.61～5.75 (m)	127.7 (CH)
10	1.64 (d, J=6.8)	13.8 (CH_3)
11	3.56 (dd, J=10.5, 5.8)	66.2 (CH_2)
	3.39～3.44 (m)	

[a] Measured in chloroform-*d*.

The known compounds **4**～**8** were identified to be dihydroaspyrone, ethyl everninate, methyl orsellinate, scirpyrone H and xylapyrone E by comparing their spectroscopic data to those reported in literatures, respectively.[8-12]

In the cytotoxicity assays, compound **2** exhibited significant cytotoxicity against the four tested human tumor cell lines SF-268, MCF-7, HepG-2 and A549 with the IC_{50} values of 0.18, 0.35, 0.22 and 0.31 μmol/L, respectively, which were more active than the positive control doxorubicin. Meanwhile, compound **3** showed moderate activity with the IC_{50} values in the range of 33 to 59 μmol/L (Table 3).

3 Conclusions

In conclusion, eight polyketides including three new ones were isolated from the deep-sea-derived fungus *Talaromyces indigoticus* FS688. Their structures were determined by spectroscopic analysis and ECD calculations. Compounds **2** and **3** exhibited potent cytotoxicity against four tested human tumor cell lines. This study will make contributions to the chemical and biological diversities of secondary metabolites from deep-sea-derived fungi.

4 Experimental section

4.1 General experimental procedures

Optical rotations and IR spectra were measured using an Anton Paar MCP-500 (Anton Paar, Graz, Austria) and a Shimadzu IR Affinity-1 spectrophotometers, respectively, meanwhile, the circular dichroism (ECD) and the UV spectra measurements were collected on a Jasco 820 spectropolarimeter at the range of 200～400 nm. 1D NMR and 2D NMR data were recorded on a 600 MHz Bruker Avance-III HD spectrometer and tetramethylsilane was used as reference. HRESIMS were measured on a Bruker maXis high resolution mass spectrometer. A Shimadzu LC-20 AT equipped with an SPD-M20A DAD detector and equipped an ACE 5 PFP-C18 column (250 mm×10.0 mm, 5 μm, 12 nm) was used for semi-separation high Pperformance liquid chromatography (HPLC), while a S-chiral A column or a CHIRAL-MD (2)-RH column (250×10.0 mm, 5 μm) was used for chiral separation (Guangzhou FLM Scientific Instrument Co., Ltd). Column chromatography material contained commercial silica gel (SiO_2; 200 ～ 300 mesh; Qingdao Marine Chemical Plant) and Sephadex LH-20 gel (Amersham Biosciences). All solvents used were analytical grade (Guangzhou Chemical Regents Company, Ltd.). The natural sea salt was purchased from Guangdong Yueyan saltern. Cells used in cytotoxicity were purchased from the cell bank of the Chinese Academy of Sciences (Shanghai, China).

Table 3 Cytotoxicity results of **1**～**3**

Compd.	IC_{50}±SD/(μmol•L^{-1})			
	SF-268	MCF-7	HepG-2	A549
1	＞100	＞100	＞100	＞100
2	0.18±0.0073	0.35±0.032	0.22±0.029	0.31±0.0081
3	33±2.6	53±14	54±2.4	58±1.7
Doxorubicin[a]	1.74±0.020	1.73±0.045	1.88±0.080	1.77±0.070

[a] Positive control.

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4.2 Fungal material.

The fungal strain FS688 was collected from deep-sea sediment in the South China Sea (118° 19.692′ N, 20° 38.982′ E; depth 2372 m) in September 2020. The strain was identified to be *Talaromyces indigoticus* by morphological traits and ITS rDNA sequence analysis. The sequence data have been submitted to GenBank with the accession number of OL774516 and the strain was deposited at the Guangdong Provincial Key Laboratory of Microbial Culture Collection and Application, Institute of Microbiology, Guangdong Academy of Sciences. Working stocks were prepared on PDA (agar 4 g/L, potato 200 g/L, glucose 20 g/L, KH_2PO_4 3 g/L, $MgSO_4$•$7H_2O$ 1.5 g/L, vitamin B_1 10 mg/L, natural sea salt 15 g/L) slants stored at 4 ℃.

4.3 Fermentation, extraction and isolation

The strain *Talaromyces indigoticus* FS688 was cultivated in PDB at 28 ℃ for 5 d to prepare the seed cultures, which was transferred into 12 Erlenmeyer flasks each containing 250 g of rice and 400 mL of H_2O with 0.3% natural sea salt. After being incubated at room temperature for 30 d, the solid rice medium was extracted three times with methanol to obtain a dark brown oily residue (20.3 g). The crude extract was subjected to silica gel chromatography column and eluted with petroleum ether/ethyl acetate in a linear gradient (V∶V=10/0 to 0/10) to afford seven fractions (Fr.1～Fr.7). The Fr.2 was further separated by Sephadex LH-20 eluting with methanol/dichloromethane (V∶V=1∶1) and silica gel chromatography column eluting with petroleum ether/ethyl acetate (V∶V=85∶15) to obtain **5** and **6**, which was purified by HPLC analysis (**5**: 3 mg, t_R=11.5 min; **6**: 4 mg, t_R=15 min; methanol/H_2O (V∶V=7∶3), 2 mL/min;). Fr.3 was subjected to repeat silica gel column chromatography and Sephdex-20 (eluting with methanol/dichloromethane, V∶V=1∶1) followed by HPLC to obtain compound **1** (2 mg, t_R=11.5 min, acetonitrile/H_2O (V∶V=6∶4), 2 mL/min). Fr.6 was separated by silica gel chromatography column eluting with petroleum ether/ethyl acetate (V∶V=8∶2 to 2∶8) to obtain five fractions (Fr.6-1～Fr.6-6). Fr.6-1 was separated by Sephadex LH-20 eluting with methanol/dichloromethane (V∶V=1∶1), silica gel chromatography column eluting with methanol/dichloromethane (V∶V=1∶100) and HPLC in turns to obtain compound **2** (3 mg, t_R=8 min, methanol/H_2O, V∶V=3∶7, 2 mL/min). Fr.6-2 was separated by silica gel chromatography column eluting with methanol/dichloromethane (V∶V=1∶100) and HPLC to obtain compounds **4** (6 mg, t_R=8 min, methanol/H_2O, V∶V=28∶72, 2 mL/min) and **8** (5 mg, t_R=19 min). Fr.6-6 was subjected to silica gel column chromatography eluting with petroleum ether/ethyl acetate (V∶V=7∶3) and then purified by HPLC to obtain compound **7** (10 mg, t_R=10 min, acetonitrile/H_2O, V∶V=6∶4, 2 mL/min). Fr.7 was subjected to Sephadex LH-20 (methanol/dichloromethane, V∶V=1∶1) and silica gel chromatography column eluting with dichloromethane/methanol (V∶V=96∶4) followed by HPLC to obtain compound **3** (1.9 mg, t_R=10 min, acetonitrile/H_2O, V∶V=2∶8, 2 mL/min).

4.4 Details of quantum chemical calculations

The ECD calculations were carried out by Spartan'14 software (Wavefunction Inc.) and Gaussian 09 program.[13] In the conformer analysis, candidates with an energy window lower than 167.2 kJ•mol^{-1} were generated and re-optimized at the rb3lyp/6-31g(d) level. Meanwhile, the frequency calculations were performed at the same level. Then, conformers with the Boltzmann distribution over 5% were chosen for ECD calculations at PBE1PBE/tzvp or cam-b3lyp/def2tzvp level with the rotatory strengths for a total of 20 excited states. The solvent effects were considered based on the self-consistent reaction field (SCRF) method with the polarizable continuum model (PCM). The final spectrum was generated by the SpecDis program[14] using a Gaussian band shape with 0.2～0.3 eV exponential half-width from dipole-length dipolar and rotational strengths.

(2-Hydroxypropan-2-yl)-6-methyl-2,3-dihydrobenzofuran-4-ol (**1**): Colorless oil; $[\alpha]_D^{25}$ +12 (c 0.05, MeOH); UV (MeOH) λ_{max} [log ε/(L•mol^{-1}•cm^{-1})]: 208 (4.64), 231 (3.91), 280 (3.15) nm; IR (KBr) v: 3352, 2974, 2922, 1629, 1606, 1512, 1456, 1355, 1240, 1215, 1159, 1122, 1002, 987, 947, 815 cm^{-1}; ^{1}H NMR and ^{13}C NMR data see Table 1; HRESIMS calcd for $C_{12}H_{15}O_3$ $[M-H]^-$ 207.1027, found 207.1020.

5-Methylhexahydrofuro[2,3-*b*]furan-2-yl-ethan-1-ol (**2**): Colorless oil; $[\alpha]_D^{25}$ +20 (c 0.01, MeOH); UV (MeOH) λ_{max} [log ε/(L•mol^{-1}•cm^{-1})]: 226 (2.58), 277 (2.72) nm; IR (KBr) v: 3441, 2970, 2929, 2873, 1454, 1381, 1016, 887, 599 cm^{-1}; ^{1}H NMR and ^{13}C NMR data see Table 1; HRESIMS calcd for $C_9H_{17}O_3$ $[M+H]^+$ 173.1172, found 173.1175; calcd for $C_9H_{16}O_3Na$ $[M+Na]^+$ 195.0992, found 195.1000.

(*E*)-2-((*Z*)-Prop-1-en-1-yl)-oct-4-ene-1,6,7-triol (**3**): Yellow oil; $[\alpha]_D^{25}$ +1.1 (c 0.05, MeOH); UV (MeOH) λ_{max} [log ε/(L•mol^{-1}•cm^{-1})]: 223 (2.48) nm; IR (KBr) v: 3334, 2918, 1647, 1436, 1404, 1373, 1261, 1018, 970, 925 cm^{-1}; ^{1}H NMR and ^{13}C NMR data see Table 2; HRESIMS calcd for $C_{11}H_{20}O_3Na$ $[M+Na]^+$ 223.1305, found 223.1310.

4.5 Cytotoxicity assay

The *in vitro* cytotoxicity assays were carried out according to our previously reported method.[15] The tested human tumor cells were injected into 96-well plates and incubated at 37 ℃ for 24 h under 5% CO_2. Then, different concentrations of compounds were added and further co-incubated for 72 h. After being stained, the cell monolayers were dissolved in Tris base solution and the OD values were recorded at 570 nm. Cisplatin was used as a positive control possessing potent cytotoxic activity. All data were obtained in triplicate.

Supporting Information NMR and HR-ESI-MS spectra of **1**～**3**, energy analysis for the conformers of **1** and **2**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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