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Two New Benzoquinone Derivatives and Two New Bisorbicillinoids were Isolated from a Marine-derived Fungus *Penicillium terrestre*

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Abstract Four new compounds were isolated from a marine-derived fungus *Penicillium terrestre*, namely 2-(2′, 3′-dihydrosorbyl)-3,6-dimethyl-5-hydroxy-1,4-benzoquinone (**1**), 3-acetonyl-2,6-dimethyl-5-hydroxy-1,4-benzoquinone (**2**), dihydrobisvertinolone (**3**), tetrahydrobisvertinolone (**4**). Their structures were established on the basis of spectroscopic methods. The absolute configurations of **3** and **4** were determined by their CD spectra. Their cytotoxic effects on P388 and A-549 cell lines were preliminarily examined by the MTT method.

Keywords *Penicillium terrestre*, benzoquinone, bisorbicillinoids, dihydrobisvertinolone, Tetrahydrobisvertinolone, cytotoxic activity

Introduction

Marine microorganisms live in a set of environments distinct from those of terrestrial fungi, thus they may produce structurally novel and biologically active secondary metabolites [1]. In our search for antitumor compounds from marine microorganisms, a fungus, identified as *Penicillium terrestre*, was isolated from marine sediments collected in Jiaozhou Bay, China. Its extract showed cytotoxicity against the tsFT210 cell line, and its chemical constituents have not been reported to our best knowledge. During the course of chromatographic separation of the ethyl acetate extract from the mycelium and broth of the fungus, using a bioassay-guided procedure with the tsFT210 cells, four new compounds (**1**∼**4**) were obtained. Compounds **3** and **4** belong to the bisorbicillinoids, which were defined by Nicolaou [2] to name a small group of dimeric sorbicillin-related natural products possessing various structures and interesting biological activities [3]. Since compounds **3** and **4** were very similar to bisvertinolone, we named them dihydrobisvertinolone and tetrahydrobisvertinolone, respectively. In this paper we report their isolation, structure elucidation, and cytotoxic activity to P388 and A-549 cell lines.

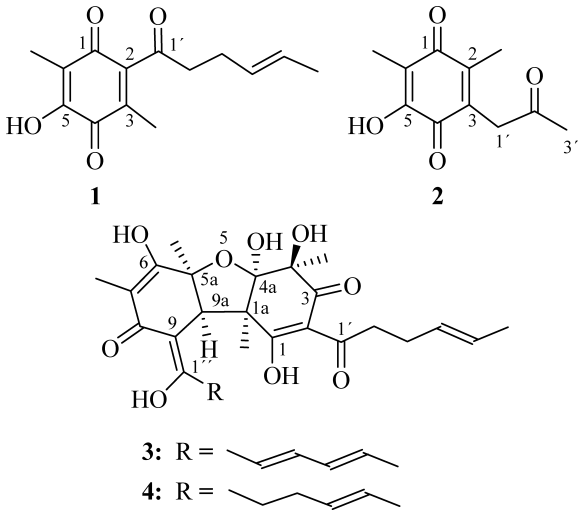

Fig. 1 Structures of compounds **1**∼**4**.

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Materials and methods

Microorganism

Penicillium terrestre was isolated from marine sediments collected in Jiaozhou Bay, China. It was preserved in China Center for Type Culture Collection (patent depositary number: CCTCC M 204077).

Fermentation

A small spoon of spores growing on potato dextrose agar slant was inoculated into a 250 ml Erlenmeyer flask containing 75 ml of sea-water based culture medium composed of glucose 2%, maltose 2%, monosodium glutamate 10%, beef extract 0.3%, KH_2PO_4 0.05%, $MgSO_4 \cdot 7H_2O$ 0.03%, and cultured at 28°C for two days on a rotary shaker at 160 rpm. Then 10 ml of the resultant seed culture was inoculated into 500 ml Erlenmeyer flasks each containing 150 ml of the above culture medium and incubated at 28°C for seven days on a rotary shaker at 160 rpm.

Extraction and Isolation

The fermented whole broth (50 liters) was filtered through cheesecloth to separate into supernatant and mycelia. The former was concentrated *in vacuo* to about a quarter of original volume and then extracted three times with ethyl acetate to give an ethyl acetate solution, while the latter was extracted three times with acetone. The acetone solution was evaporated under reduced pressure to afford an aqueous solution. The aqueous solution was extracted three times with ethyl acetate to give another ethyl acetate solution. Both the ethyl acetate solutions were combined and concentrated *in vacuo* to give a crude extract (58.0 g).

The crude extract (58.0 g) was applied to a silica gel (200~300 mesh) column packed in petroleum ether. The column was then eluted in gradient ratios with petroleum ether - chloroform and chloroform - methanol, respectively. The active fraction that eluted with petroleum ether - chloroform (1 : 3) was further chromatographed on silica gel using petroleum ether - ethyl acetate (20 : 1~1 : 1). Compounds **1** (15 mg) and **2** (26 mg) were afforded as crystalline solids from the fractions eluted with petroleum ether - ethyl acetate, 5 : 1 and 4 : 1, respectively. Another active fraction that eluted with chloroform - methanol (50 : 1) was then applied to Sephadex LH-20 using chloroform - methanol (1 : 1) as eluting solvent. The active subfraction was separated by semipreparative HPLC on an ODS column using methanol - water (80 : 20) as eluting solvent to yield compounds **3** (25 mg) and **4** (40 mg).

Biological Assay

Cytotoxic activity was evaluated by the MTT [4] method, using P388 and A-549 cell lines. The cell lines were grown in RPMI-1640 supplemented with 10% FBS under a humidified atmosphere of 5% CO_2 and 95% air at 37°C. Portions of those cell suspensions, 200 μl, at a density of 5×10^4 cell ml^{-1} were plated in 96 well microtiter plates and incubated for 24 hours under the above conditions. Then 2 μl of the test compound solutions (in DMSO) at different concentrations was added to each well and further incubated for 72 hours under the same conditions. Finally, 20 μl of MTT solution (5 mg/ml in RPMI-1640 medium) was added to each well and incubated for 4 hours. Medium containing MTT, 150 μl, was removed from each well and gently replaced by DMSO to dissolve any formazan crystals that formed. Absorbance was then determined on SPECTRA MAX PLUS plate reader at 540 nm. The IC_{50} values were obtained using the Bliss method. The IC_{50} values were obtained using the Bliss method.

Results and Discussion

Physico-chemical Properties

Compound **1**: orange needles; mp 127~129°C; HREIMS *m/z* 248.1032 (calcd for $C_{14}H_{16}O_4$, 248.1048); UV (MeOH) λ_{max} nm (log ε) 211 (4.23), 269 (4.10); IR ν_{max} cm^{-1} (KBr) 3286, 2955, 2919, 1715, 1655, 1639, 1623, 1390, 1378, 1354, 1316, 1288, 1177, 1164, 1071, 919, 731.

Compound **2**: orange needles; mp 118°C (dec.); HRESIMS *m/z* 209.0807 $[M+H]^+$ (calcd for $C_{11}H_{13}O_4$, 209.0814); UV (MeOH) λ_{max} nm (log ε) 267 (4.08); IR ν_{max} cm^{-1} (KBr) 3288, 1715, 1655, 1639, 1625, 1379, 1356, 1317, 1288, 1175, 1071, 731.

Compound **3**: yellowish amorphous powder; mp 115~119°C; $[\alpha]_D^{20}$ −668° (*c* 0.24, MeOH); HRESIMS *m/z* 515.2283 $[M+H]^+$ (calcd for $C_{28}H_{35}O_9$, 515.2281); UV (MeOH) λ_{max} nm (log ε) 225 (4.57), 271 (4.61), 385 (4.57); IR ν_{max} cm^{-1} (KBr) 3425, 2986, 2938, 1670, 1616, 1555, 1445, 1412, 1378, 1347, 1205, 1025, 992, 968, 942.

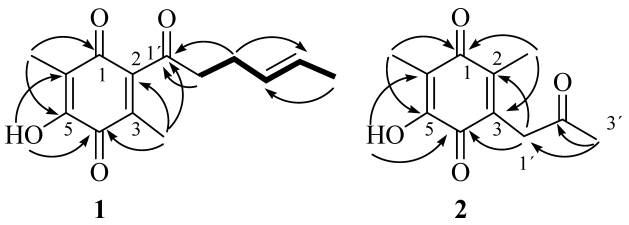
Compound **4**: yellowish amorphous powder; mp 82~87°C; $[\alpha]_D^{20}$ −371° (*c* 0.36, MeOH); HRESIMS *m/z* 539.2214 $[M+Na]^+$ (calcd for $C_{28}H_{36}O_9Na$, 539.2257); UV (MeOH) λ_{max} nm (log ε) 228 (4.05), 267 (4.06), 336 (4.01); IR ν_{max} cm^{-1} (KBr) 3417, 2992, 2935, 1670, 1598, 1446, 1378, 1343, 1210, 1025, 966, 933.

Structure Determination

Compound **1**: Its molecular formula, $C_{14}H_{16}O_4$, was established by HREIMS, which was in agreement with its ^1H and ^{13}C NMR data. In the ^1H NMR spectrum the signals

at δ 5.48 (1H, m), 5.43 (1H, dt, 15.06, 7.32), 2.72 (2H, t, 7.32), 2.35 (2H, brq, 7.32) and 1.64 (3H, dd, 5.88, 1.44) revealed a dihydrosorbyl group [5]. The *E* configuration of the double bond in the dihydrosorbyl chain could be deduced by the magnitude of the coupling constant (Table 1), and its position at C-4′ was obtained from the COSY and HMBC spectra (Fig. 2), which was also supported by the splitting of H-6′ (Table 1).

The ^{13}C NMR spectrum showed fourteen carbons, three carbonyls, four sp^2 quaternary carbons, two olefinic methines, two methylenes and three methyls. Except the carbons in the dihydrosorbyl residue and the other two methyls, the remaining six carbons formed benzoquinone ring, which was confirmed by the absorptions [6] (1655, 1639 and 1623 cm^{-1}) in the IR spectrum and the signals in the ^{13}C NMR spectrum (Table 1). The positions of hydroxyl and two methyls were finally determined by the HMBC experiment (Fig. 2). The dihydrosorbyl group attachment to C-2 was self-evident, which was also corroborated by the weak correlation of CH_3-3 with C-1′, though no correlated peak between H-2′ and C-2 was observed in the HMBC spectrum. This completed the structure of **1**.



1 **2**

Fig. 2 Key COSY and HMBC correlations for **1** and **2**.

Compound **2**: Its ^{1}H and ^{13}C NMR data showed three carbonyls, four sp^2 quarternary carbons, one methylene, three methyls and a hydroxyl. On the basis of these data, and on HRESIMS analysis, **2** was assigned the molecular formula $C_{11}H_{12}O_4$. Detailed analysis of its IR absorptions and ^{13}C NMR data revealed that **2** was also a benzoquinone derivative. An acetonyl residue could be deduced from the HMBC correlations of CH_3-3′ with C-1′ and C-2′ (Fig. 2). Its connection to C-3 could be proved by the HMBC correlations of H-1′ with C-2, C-3 and C-4. The positions of the other two methyls and one hydroxyl were determined on the basis of the HMBC data (Fig. 2). So the structure of **2** was obtained.

Compound **3**: The HRESIMS revealed its molecular formula to be $C_{28}H_{34}O_9$, which corresponded well to its ^{1}H and ^{13}C NMR data. The IR absorptions at 3425, 1670, 1616 and 1555 cm^{-1}, were suggestive of the presence of hydroxyl, α,β-unsaturated carbonyl and two enolized diketones [7], which were proved by the very low field chemical shifts (δ: 18.21 and 16.32) of two hydroxyls in the ^{1}H NMR spectrum.

In addition, the ^{1}H NMR spectrum displayed the presence of a sorbyl group [7, 8] [6.39 (1H, d, 14.88), 7.33 (1H, dd, 14.88, 11.13), 6.29 (1H, m), 6.15 (1H, dq, 14.82, 6.60) and 1.88 (3H, d, 6.60)] and a dihydrosorbyl group [5,

Table 1 ^{1}H and ^{13}C NMR data for **1** and **2** ($CDCl_3$, 600 and 150 MHz, TMS, δ in ppm)

No	**1**		**2**	
	δ_H (*J* in Hz)	δ_C	δ_H	δ_C
1		186.2		187.2
2		136.1		146.0
3		144.5		133.5
4		183.6		182.6
5		151.1		150.6
6		116.9		117.5
CH_3-3 (2 for **2**)	1.96 (3H, s)	11.8	2.01 (3H, s)	13.2
CH_3-6	1.94 (3H, s)	7.8	1.95 (3H, s)	8.2
1′		203.0	3.67 (2H, s)	40.5
2′	2.72 (2H, t, 7.32)	44.1		203.1
3′	2.35 (2H, br q, 7.32)	26.0	2.28 (3H, s)	30.1
4′	5.43 (1H, dt, 15.06, 7.32)	128.9		
5′	5.48 (1H, m)	126.4		
6′	1.64 (3H, dd, 5.88, 1.44)	17.8		
OH	6.97 (1H, s)		6.95 (1H, s)	

Table 2 ^{1}H and ^{13}C NMR, and HMBC data for **3** and **4** ($CDCl_3$, 600 and 150 MHz, TMS, δ in ppm)

No	**3**			**4**		
	δ_H (*J* in Hz)	δ_C	HMBC (H→C)	δ_H (*J* in Hz)	δ_C	HMBC (H→C)
1		197.4			197.5	
2		108.2			108.2	
3		196.3			196.3	
4		78.9			78.8	
4a		104.0			104.0	
5a		79.9			79.9	
6		163.7			163.5	
7		110.6			109.8	
8		191.1			190.4	
9		99.5			98.8	
9a	3.81 (1H, s)	54.2	CH_3-1a, 1, 1a, 5a, 6, 8, 9, 1″, CH_3-5a	3.71 (1H, s)	54.8	CH_3-1a, 1, 1a, 5a, 6, 8, 9, 1″, CH_3-5a
1a		58.7			58.4	
CH_3-1a	1.49 (3H, s)	18.2	1, 1a, 4a, 9a	1.50 (3H, s)	18.2	1, 1a, 4a, 9a
CH_3-4	1.41 (3H, s)	23.1	3, 4, 4a	1.40 (3H, s)	23.1	3, 4, 4a
CH_3-5a	1.52 (3H, s)	25.7	5a, 6, 9a	1.48 (3H, s)	25.4	5a, 6, 9a
CH_3-7	1.52 (3H, s)	7.0	6, 7, 8	1.50 (3H, s)	6.9	6, 7, 8
1′		202.8			202.7	
2′	2.89 (1H, m); 3.06 (1H, m)	38.8	1′, 3′, 4′	2.89 (1H, m); 3.05 (1H, m)	38.7	1′, 3′, 4′
3′	2.24 (1H, m); 2.35 (1H, m)	28.0	2′, 4′, 5′	2.24 (1H, m); 2.34 (1H, m)	28.0	2′, 4′, 5′
4′	5.46 (1H, m)	129.0	3′, 6′	5.47 (1H, m)	129.1	3′, 6′
5′	5.50 (1H, m)	126.4	3′, 6′	5.50 (1H, m)	126.4	3′, 6′
6′	1.63 (3H, d, 5.82)	17.9	4′, 5′	1.64 (3H, dd, 1.62, 7.02)	17.8	4′, 5′
1″		170.3			180.4	
2″	6.39 (1H, d, 14.88)	119.8	1″, 3″, 4″	2.49 (1H, m); 2.64 (1H, m)	32.9	1″, 3″, 4″
3″	7.33 (1H, dd, 14.88, 11.13)	139.8	1″, 4″, 5″	2.41 (2H, m)	29.7	1″, 2″, 4″
4″	6.29 (1H, m)	130.9	2″, 3″, 5″, 6″	5.47 (1H, m)	129.3	3″, 6″
5″	6.15 (1H, dq, 14.82, 6.60)	137.8	3″, 4″, 6″	5.50 (1H, m)	126.5	3″, 6″
6″	1.88 (3H, d, 6.60)	18.8	4″, 5″	1.64 (3H, dd, 1.62, 7.02)	17.9	4″, 5″
OH-4	4.80 (1H, s)		3, 4			
OH-4a	4.64 (1H, s)		1a, 4a			
OH-6	6.98 (1H, s)		7			
OH-1	18.21		1a, 1, 2, 1′, 2′	18.20 (1H, s)		1, 1a, 2, 1′, 2′
OH-1″	16.32		8, 9, 1″, 2″	16.64 (1H, s)		1″, 2″, 8, 9

9] [(2.89 (1H, m), 3.06 (1H, m), 2.24 (1H, m), 2.35 (1H, m), 5.46 (1H, m), 5.50 (1H, m) and 1.63 (3H, d, 5.82)], which were also confirmed by the ^{1}H-^{1}H COSY and HMBC spectra. The *E*, *E* configuration of the two double bonds in the sorbyl residue was evident from the large coupling constants. The *E* configuration of the double bond in the dihydrosorbyl chain was confirmed by the correlation of CH_3-6′ with H-4′ in the NOESY spectrum.

The ^{13}C NMR spectrum showed 28 carbons. Careful analysis and comparison of the ^{13}C NMR data with bisvertinolone [7, 9, 10] revealed that compound **3** should have the same hydrodibenzofuran core as that of bisvertinolone, which was verified by the HMBC experiment (Table 2). That the sorbyl group was bound to C-9 was ascertained from the correlations of OH-1″ with C-8, C-9, C-1″ and C-2″, and H-9a with C-8, C-9 and C-1″. Compared with C-1″ (170.3), C-8 (191.1) is more ketonic in nature, and thus the enolic hydroxyl was arranged at C-1″ [8]. Furthermore, the correlations of OH-1 with C-1a, C-1, C-2, C-1′, and C-2′ supported the dihydrosorbyl attachment on C-2 and that enolization of the 1,3-dicarbonyl system occurred between C-1 and C-1′, not

between C-1′ and C-3.

In the NOESY spectrum the cross peaks of H-9a with CH_3-1a, CH_3-5a and H-2″, and CH_3-4 with CH_3-1a indicated CH_3-1a, CH_3-4, CH_3-5a and H-9a should be on the same side of the molecule. The configuration of OH-4a in **3** should be identical with bisvertinolone from the point of biogenesis [11]. But there were a few arguments about the configuration of OH-4a in bisvertinolone. Kontani [10] thought OH-4a should be *trans* to CH_3-1a and CH_3-4 from the consideration of CPK models. On the other hand Andrade [7] assigned OH-4a as *cis* to CH_3-1a on the basis of the enhanced stability of a *cis* 5~6 ring junction over a *trans* 5~6 ring junction. Moreover, Abe [11] proved OH-4a was *cis* to CH_3-1a, based on the elucidation of the biosynthesis of bisvertinolone from oxosorbicillinol and sorbicillinol. But judging from molecular models we found that whether OH-4a was *trans* or *cis* to CH_3-1a, the distance between CH_3-1a and CH_3-4 was close enough for the NOE to be observed between the two methyls. So we assigned OH-4a as *cis* to CH_3-1a in **3**.

In the CD spectrum **3** showed strong splitting Cotton effect at 372 nm ($\Delta\varepsilon-62$) and 296 nm ($\Delta\varepsilon+60$), which was very similar to bisvertinolone [7, 9, 10]. Therefore, the absolute stereochemistry of **3** was assigned as 1a *R*, 4 *R*, 4a *R*, 5a *S* and 9a *R*.

Compound **4**: Its molecular formula was determined to be $C_{28}H_{36}O_9$ by HRESIMS, which was well consistent with its ^1H and ^{13}C NMR data. The IR spectrum of **4** showed absorptions at 3417 (hydroxyl), 1670 (α,β-unsaturated carbonyl) and 1598 cm^{-1} (enolized diketone), which was very similar to bisvertinolone and **3**. Detailed analysis and comparison of the ^1H and ^{13}C NMR data with those of **3** revealed that **4** possesses the same planar structure as **3**, except that the sorbyl group in **3** corresponds to a dihydrosorbyl group in **4**. The conclusion was validated by the COSY and HMBC experiments (Table 2). The stereochemistry of two dihydrosorbyl residues was assigned as *E* on the basis of the NOESY correlations of H-6′ with H-4′ and H-6″ with H-4″.

The NOESY correlations (H-9a with CH_3-1a, CH_3-5a and H-2″, and CH_3-1a with H-2″, H-9a and CH_3-4) and the CD absorptions [352 nm ($\Delta\varepsilon-100$) and 293 nm ($\Delta\varepsilon+85$)] revealed the absolute stereochemistry of **4** is the same as that of **3**.

Cytotoxic Activities

The cytotoxic effects of compounds **1**~**4** were preliminarily evaluated in P388 and A-549 cell lines. VP16 was used as positive control. As shown in Table 3, compound **3** displayed much more potent cytotoxic activities compared with the two benzoquinone derivatives.

Table 3 The activities (IC_{50}, μM) of compounds 1~4 on cancer cell lines

	1	**2**	**3**	**4**	VP16
P388	15.7	10.5	1.7	>100	0.064
A-549	5.3	7.6	0.52	16.7	1.4

Notably, compound **3** showed higher activity than that of **4**, suggesting that the conjugated double bond in side chain might favor the activity of this kind of compound.

In fact, some intriguing biological activities for several sorbicillinoids have hitherto been found, including inhibition of the biosynthesis of β-1,6-glucan [10] and the production of tumor necrosis factor α (TNF-α) [12] induced by lipopolysaccharide, and the property of scavenging free radicals as well [13]. That compounds **3** and **4**, new members of bisorbicillinoids, possessed anti-proliferative action in P388 and A-549 cells suggested that bisorbicillinoids might be investigated as potential anticancer agents. Detailed studies on their antitumor activities and related mechanisms of action are being undertaken.

Experimental

Melting points were measured using a Yanaco MP-500D micro-melting point apparatus and were uncorrected. Optical rotations were obtained on a JASCO P-1020 digital polarimeter. UV spectra were recorded on Beckmen DU® 640 spectrophotometer. IR spectra were taken on a NICOLET NEXUS 470 spectrophotometer in KBr discs. ^1H, ^{13}C NMR and DEPT spectra and 2D-NMR were recorded on a JEOL Eclips-600 spectrometer using TMS as internal standard and chemical shifts were recorded as δ values. EI-MS and ESI-MS were measured on Autospec-Ultima ETOF and Esquir LC mass spectrometers, respectively. Semiprepartive HPLC was performed using an ODS column (Capcell Park C_{18}, 20×250 mm, 5 μm, 4 ml/minute).

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