

ORIGINAL ARTICLE

Lobophorins E and F, new spirotetronate antibiotics from a South China Sea-derived *Streptomyces* sp. SCSIO 01127

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The strain SCSIO 01127, isolated from the South China Sea sediment, was identified as a member of *Streptomyces* by the 16S rDNA sequence analysis. Two new spirotetronate antibiotics lobophorins E (1) and F (2), along with two known analogs lobophorins A (3) and B (4), were isolated from *Streptomyces* sp. SCSIO 01127. Their structures were elucidated on the basis of detailed IR, NMR and MS spectroscopic analyses. The new compound lobophorin F (2) showed antibacterial activities against *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 with MIC values of 8 $\mu\text{g ml}^{-1}$ for both the strains, better than that of lobophorin B (4). Lobophorin F (2) also displayed better cytotoxic activities than lobophorin B (4), with IC₅₀ of 6.82, 2.93 and 3.16 μM against SF-268, MCF-7 and NCI-H460, respectively.

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INTRODUCTION

In recent years, more and more novel genera and species of marine actinomycetes have been isolated from sediments of the South China Sea,^{1–5} suggesting South China Sea to be a rich source for exploring new marine actinomycete taxa. In the past two decades, marine actinomycetes are emerging as the most prolific new sources for novel drug discovery and have produced lots of secondary metabolites exhibiting excellent biological activities.^{6–8} Recently, *Marinactinospora thermotolerans* SCSIO 00606, a newly identified novel genus from the South China Sea, was found to produce new γ -pyrones, marinactinones A–C, which showed moderate antitumor activity and weak DNA topoisomerase II-inhibiting activity.⁹ This discovery inspires our particular interests in exploring the numerous actinobacterial strains collected from the South China Sea for their potential in producing novel compounds. During our continuous searching efforts, a deep-sea actinobacterial strain SCSIO 01127 caught our attention, for that the organic extract of the fermentation broth of this strain showed excellent antibacterial activities. Here we report the preliminary characterization of the strain SCSIO 01127 as a member of the *Streptomyces* genus by 16s rDNA analysis, the isolation and structural elucidation of four spirotetronate antibiotics. Two compounds were identified to be novel lobophorin analogues, designated lobophorins E (1) and F (2), and the other two were found to be lobophorins A (3) and B (4).¹⁰ Interestingly, lobophorin F (2) exhibited better cytotoxic

activities against three tumor cell lines (SF-268, MCF-7 and NCI-H460) and better antibacterial activities than lobophorin B (4).

MATERIALS AND METHODS

General experimental procedures

Materials for column chromatography were silica gel (100–200 mesh; 300–400 mesh; Jiangyou Silica gel development, Yantai, PR China), Sephadex LH-20 (40–70 μm ; Amersham Pharmacia Biotech AB, Uppsala, Sweden), and YMC*-GEL ODS-A (12 nm S-50 μm ; YMC Company, Kyoto, Japan). TLC(0.1–0.2 mm or 0.3–0.4 mm) was conducted with pre-coated glass plates (silica gel GF₂₅₄, 10–40 nm, Jiangyou Silica gel development). Medium-pressure liquid chromatography was performed on automatic flash chromatography (EZ Purifier III, Leisure Science, Shanghai, China) with monitor wavelength of 210 nm and collector wavelength of 263 nm. Mass spectral data were obtained on a quadrupole-time-of-flight MS (Waters, Milford, MA, USA) for high-resolution FAB-MS. The optical rotation was recorded on a 341 Polarimeter (Perkin Elmer, Norwalk, CT, USA). UV spectra were obtained during detection of the monomer compounds on a Varian ProStar 210 HPLC (Varian Australia Pty., Ltd., Mulgrave, VIC, Australia). IR spectra were obtained in KBr with a FT-IR EQUINOX 55 Bruker (Bruker Optik GmbH, Ettlingen, Germany). ¹H, ¹³C NMR and 2D NMR spectra were recorded on a Bruker AV-500 NMR spectrometer (Bruker Biospin GmbH, Rheinstetten, Germany) with tetramethylsilane (δ 0 p.p.m.) as the internal standard. ¹H NMR data were reported as follows: chemical shift (multiplicity: singlet (s), doublet (d), triplet (t), and multiplet (m); coupling constants: Hz); ¹³C NMR data were reported as follows: chemical shift (quaternary carbon (s), methine (d), methylene (t)

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and methyl (q)). Deuterated NMR solvents were purchased from Cambridge Isotopes (Andover, MA, USA).

Isolation, characterization and fermentation of the strain

SCSIO 01127

The strain SCSIO 01127 was isolated from a sediment sample (E 111°54.693', N 08°56.003') at the depth of 1350 m in the South China Sea from an open voyage in July 2007, after incubation at 28 °C for 2 weeks on Gauze's Medium No. 1 (soluble starch 2%, KNO₃ 0.1%, K₂HPO₄ 0.05%, MgSO₄·7H₂O 0.05% and FeSO₄·7H₂O 0.01% at pH 7.4), and was deposited in the type culture collection of Center for Marine Microbiology, Research Network of Applied Microbiology, South China Sea Institute of Oceanology and Chinese Academy of Sciences, Guangzhou, China. Genomic DNA isolation, PCR amplification of 16S rDNA, sequence comparison and phylogenetic tree construction of the strain SCSIO 01127 were performed as described previously.¹ A single colony of SCSIO 01127 was inoculated into 50 ml of seed medium (soybean meal 0.3%, yeast extract 0.3%, trehalose 1%, proline 0.1%, beef extract 0.3%, glycerol 0.6%, K₂HPO₄ 0.03%, MgSO₄·7H₂O 0.05%, FeSO₄·7H₂O 0.01%, CaCO₃ 0.2% and sea salt 3% at pH 7.4 before sterilization) in 250-ml Erlenmeyer flasks, and was cultured on a rotary shaker at 200 r.p.m., 28 °C for 2 days. A total of 5 ml of seed cultures were transferred into 50 ml production medium (the same as the seed medium) in 250 ml Erlenmeyer flasks, and were cultured on a rotary shaker at 200 r.p.m., 28 °C for 5 days.

Isolation of lobophorins from SCSIO 01127

The 4.5-l fermentation broth was extracted four times with 17 l butanone to afford residue A after removal of the solvent. The mycelia cake was extracted three times with 4 l acetone. After removing acetone, the residue was re-extracted by 4 l butanone to afford residue B upon removal of the solvent. Residues A and B were combined as the crude extract for further isolation. The crude extract was subjected to silica gel column chromatography (300–400 mesh, 150 g), and eluted with CHCl₃/CH₃OH (100:0–5:1) to give three fractions (Fr.1–Fr.3). Fr.1 was subjected to Sephadex LH-20, and eluted with CHCl₃/CH₃OH (1:1), to give two sub-fractions (Fr.1-1 and Fr.1-2). Fr.1-1 was first purified by preparative TLC on a silica gel plate (20×20 cm) developed with CHCl₃/CH₃OH (30:1), and then by semi-preparative HPLC on a Varian Star Workstation, using a reverse-phase column C18 (YMC*GEL ODS-A, 120A S-5 μm, 250×10 mm) with UV detection at 263 nm, to afford compound 2 (11.5 mg). The following HPLC program was used: solvent A, 10% acetonitrile in water; solvent B, 90% acetonitrile in water; 40% B to 100% B (linear gradient, 0–9 min), 100% B (9–17 min), 100% B to 40% B (17–18 min), 40% B (18–26 min); the flow rate was 2.5 ml min⁻¹. Fr.1-2 was purified by semi-preparative C18 reverse-phase medium-pressure liquid chromatography (YMC*GEL ODS-A, 12 nm S-50 μm, 30×2.5 cm), with a linear gradient elution (CH₃OH/H₂O 10–90%, 15 ml min⁻¹, 160 min). The desired fractions were further purified by semi-preparative HPLC to get compound 1 (2.5 mg), under the above mentioned conditions with a different developing program: 40% B to 100% B (linear gradient, 0–11 min), 100% B (11–16 min), 100% B to 40% B (16–17 min) and 40% B (17–23 min).

Fr. 2 was subjected to Sephadex LH-20 chromatography, and eluted with CHCl₃/CH₃OH (1:1). The desired fractions were further purified by medium-pressure liquid chromatography (YMC*GEL ODS-A, 12 nm S-50 μm, 30×2.5 cm). After elution with a linear gradient (CH₃OH/H₂O 10–60%, 15 ml min⁻¹, 160 min), compound 3 (56.2 mg) was obtained. Fr. 3 was first separated by Sephadex LH-20 chromatography with CHCl₃/CH₃OH (1:1) elution, and then by medium-pressure liquid chromatography (YMC*GEL ODS-A, 12 nm S-50 μm, 30×2.5 cm), with a linear gradient elution (CH₃OH/H₂O 15–95%, 15 ml min⁻¹, 160 min), to afford compound 4 (210.6 mg).

Structure determination

Lobophorin E (1): White powder, $[\alpha]_D^{20}$ -20.0 ($c=0.38$, MeOH), UV (in CH₃CN: H₂O: trifluoroacetic acid) 214.9, 263.1 nm. IR (KBr) 3522, 3439, 2932, 1734, 1627, 1545 and 1454 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) and ¹³C NMR (125 MHz, CDCl₃), see Table 1; HR-MS m/z 1169.5874 (calcd for C₆₁H₈₉N₂O₂₀, [M-H]⁻ 1169.6009); ESI-MS m/z 1194.1 [M+Na]⁺, 1170.2 [M-H]⁻.

Lobophorin F (2): White powder, $[\alpha]_D^{20}$ -60.0 ($c=0.76$, MeOH), UV (in CH₃CN: H₂O: trifluoroacetic acid) 210.6, 264.1 nm. IR (KBr) 3440, 2934, 1737, 1629, 1545 and 1454 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) and ¹³C NMR (125 MHz, CDCl₃), see Table 1; HR-MS m/z 1049.5160 (calcd for C₅₄H₇₈N₂O₁₇Na, [M+Na]⁺ 1049.5198); ESI-MS m/z 1050.0 [M+Na]⁺, 1026.0 [M-H]⁻.

Lobophorin A (3): White powder, ESI-MS: m/z 1157.8 [M+H]⁺, 1155.9 [M-H]⁻.

Lobophorin B (4): White powder, ¹H NMR (500 MHz, CDCl₃) and ¹³C NMR (125 MHz, CDCl₃), see Table 1; ESI-MS m/z 1210.3 [M+Na]⁺, 1186.1 [M-H]⁻.

Biological activity

MIC values of lobophorins (1–4) were determined against three bacterial strains, including *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Bacillus thuringiensis* SCSIO BT01, according to previously described methods.¹¹ Cytotoxicities of lobophorins F (2), A (3) and B (4) were assayed against three tumor cell lines, including MCF-7 cells (human breast adenocarcinoma cell line), NCI-H460 (human non-small cell lung cancer cell line) and SF-268 (human glioma cell line). Assays were performed as described previously.¹²

RESULTS AND DISCUSSION

Taxonomy of the producing strain

The producing strain SCSIO 01127, with a colonial morphology characteristic for actinobacteria, was isolated from deep-sea sediment of the South China Sea. The 16S rDNA of SCSIO 01127 was PCR amplified, sequenced and submitted to GenBank (accession number is JF794566). The phylogenetic tree generated by a neighbor-joining method clearly revealed the evolutionary relationship of the strain SCSIO 01127 with a group of *Streptomyces* species (Figure 1). Blast search showed that the new isolate had the highest similarities to *Streptomyces olivaceus* NBRC 12805T (AB249920) (100%) and *Streptomyces pactum* NBRC 13433T (100%). Thus, this strain was designated as *Streptomyces* sp. SCSIO 01127.

Structural elucidation

Compound 3 was determined to be lobophorin A by comparing the ¹H and ¹³C NMR spectra data with those previously reported.¹⁰ Compound 4 was determined to be lobophorin B by comparing ¹H, ¹³C, ¹H-¹H COSY and HMBC NMR spectral data with those reported in literature (Table 1).¹⁰ The molecular formula of compound 1 was established as C₆₁H₈₉N₂O₂₀ by HR-MS (m/z 1169.5874 [M-H]⁻, calcd 1169.6009). The IR spectrum of 1 showed absorption bands characteristic of hydroxyl (3522 and 3439 cm⁻¹), methylene (2932 cm⁻¹), carboxyl (1734 cm⁻¹) and olefinic groups (1627, 1545 and 1454 cm⁻¹). The ¹H and ¹³C NMR spectra of 1 were almost identical to those of lobophorin B (4).¹⁰ The difference between 1 and 4 is that the oxygenated methylene (δ_H 4.15 (2H, m, H-32) and δ_C 64.7 (t, C-32)) in 4 was replaced by a methyl singlet (δ_H 1.80 (3H, s, Me-32) and δ_C 21.8 (q, Me-32)) in 1, indicating the absence of C-32-OH in 1 (Table 1). Consistently, the HMBC correlations from proton signals of the methyl singlet H₃-32 to C-21, C-22 and C-23 confirmed the location of this methyl group at C-32 in 1. On the basis of these data, 1 was identified to be 32-deshydroxyl-lobophorin B, designated as lobophorin E (Figure 2).

According to the HR-MS analysis, the molecular formula of compound 2 (m/z 1049.5160 [M+Na]⁺, calcd 1049.5198) was established as C₅₄H₇₈N₂O₁₇. The IR spectrum of 2 showed absorption bands corresponding to hydroxyl (3440 cm⁻¹), methylene (2934 cm⁻¹), carboxyl (1737 cm⁻¹) and olefinic groups (1629, 1545 and 1454 cm⁻¹). In comparison of the ¹H and ¹³C NMR spectra data

Table 1 ^1H and ^{13}C NMR assignment of compound 1, 2 and 4 (*J* in Hz within parentheses) (measured at 500 MHz in CDCl_3)

No.	1		2		4	
	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}
1		167.3 s		167.3 s		167.2 s
2		101.9 s		101.9 s		101.8 s
3		206.3 s		206.3 s		206.3 s
4		50.9 s		51.0 s		51.0 s
5	2.01 m	43.1 d	1.98 m	43.4 d	1.98 (t, 9.0)	43.1 d
6	1.60 m	31.3 d	1.58 m	31.2 d	1.55 m	31.3 d
7	1.53 m, 1.61 m	41.7 t	1.50 (d, 9.0); 1.59 m	41.9 t	1.48 (d, 8.5); 1.55 m	41.7 t
8	2.33 m	34.4 d	2.28 m	34.5 d	2.19 m	34.4 d
9	3.56 m	84.2 d	3.44 (dd, 6.0, 11.0)	86.7 d	3.42 (dd, 5.5, 11.0)	84.0 d
10	2.16 m	38.5 d	2.14 m	38.2 d	2.06 m	38.5 d
11	5.72 (d, 10.0)	125.9 d	5.76 (d, 10.5)	125.9 d	5.70 (d, 10.5)	126.0 d
12	5.39 m	126.5 d	5.40 m	126.6 d	5.36 m	126.4 d
13	3.50 m	53.1 d	3.48 m	53.1 d	3.45 m	53.2 d
14		135.7 s		135.7 s		135.8 s
15	5.19 brs	123.5 d	5.18 brs	123.5 d	5.15 brs	123.4 d
16	1.26 m, 2.38 m	31.2 t	1.56 m, 2.33 m	31.2 t	1.22 m, 2.31 m	30.0 t
17	4.17 m	78.9 d	4.17 brs	78.9 d	4.21 brs	78.2 d
18		136.8 s		136.7 s		137.1 s
19	5.16 brs	119.9 d	5.16 brs	119.9 d	5.12 (d, 10.0)	119.2 d
20	3.56 m	40.4 d	3.56 (d, 10.5)	40.4 d	3.60 (d, 10.0)	40.2 d
21	5.23 s	120.6 d	5.22 s	120.6 d	5.50 s	121.5 d
22		137.8 s		137.8 s		141.4 s
23	2.39 m	31.9 d	2.36 m	31.9 d	2.67 (t, 7.5)	28.0 d
24	1.79 m, 2.36 m	35.5 t	1.79 m, 2.32 m	35.5 t	1.83 (d, 14.0), 2.36 (dd, 2.5, 14.0)	35.4 t
25		83.3 s		83.3 s		83.3 s
26		201.9 s		201.7 s		201.7 s
27	1.62 s	15.1 q	1.61 d	15.1 q	1.60 s	15.1 q
28	0.65 (d, 4.5)	22.2 q	0.64 (d, 4.5)	22.2 q	0.63 (d, 4.5)	22.3 q
29	1.08 (d, 7.0)	14.2 q	1.13 (d, 7.0)	14.6 q	1.08 (d, 7.0)	14.2 q
30	1.33 s	13.8 q	1.33 s	13.8 q	1.31 s	13.8 q
31	1.39 s	15.1 q	1.37 s	15.1 q	1.39 s	15.1 q
32	1.80 s	21.8 q	1.78 s	21.8 q	4.20 m	65.0 t
33	1.29 (d, 6.5)	20.2 q	1.28 (d, 6.5)	20.2 q	1.31 (d, 7.0)	20.2 q
A-1	4.90 s	98.0 d	4.79 (d, 4.5)	99.1 d	4.73 (d, 4.0)	98.0 d
A-2	1.61 m, 2.38 m	30.1 t	1.86 m, 2.25 m	33.4 t	1.68 m, 2.28 m	30.9 t
A-3	4.01 m	66.5 d	4.02 m	74.1 d	3.99 m	66.5 d
A-4	3.16 (dd, 2.8, 9.8)	71.9 d	3.30 (d, 6.5)	72.4 d	3.30 m	71.6 d
A-5	3.82 m	65.4 d	4.04 m	65.0 d	3.99 m	65.4 d
A-6	1.32 (d, 6.0)	18.0 q	1.29 (d, 5.0)	17.7 q	1.24 (d, 5.5)	18.0 q
B-1	5.13 m	91.0 d	5.07 (d, 2.5)	96.5 d	5.11 (d, 4.0)	91.1 d
B-2	1.92 m, 2.31 m	34.2 t	1.96 m, 2.24 m	35.3 t	1.90 m, 2.09 m	34.2 t
B-3	4.34 m	65.1 d	3.99 m	66.9 d	4.21 m	65.0 d
B-4	3.24 (dd, 3.0, 9.5)	82.2 d	3.18 (dt, 2.5, 9.5)	72.5 d	3.23 (dd, 2.8, 9.3)	82.2 d
B-5	4.03 m	62.1 d	3.94 m	65.6 d	4.00 m	62.1 d
B-6	1.30 (d, 6.5)	17.8 q	1.32 (d, 6.0)	17.74 q	1.19 (d, 6.5)	17.8 q
C-1	D4.92 s	98.3 d			4.90 (dd, 2.0, 9.5)	98.3 d
C-2	1.68 m, 2.15 m	36.7 t			1.63 m, 2.14 m	36.8 t
C-3	4.23 m	64.0 d			4.24 m	64.0 d
C-4	2.84 (dd, 2.5, 9.5)	82.2 d			2.83 (dd, 3.0, 9.5)	82.2 d
C-5	3.77 m	68.4 d			3.74 m	68.4 d
C-6	1.27 (d, 6.5)	18.3 q			1.23 (d, 6.0)	18.3 q
C-7	3.41 s	57.4 q			3.40 s	57.4 q
D-1	4.46 (d, 9.5)	97.4 d	4.44 (d, 9.5)	97.4 d	4.43 (dd, 1.5, 10.0)	96.7 d
D-2	1.62 (d, 15.0), 2.81 (d, 15.0)	35.8 t	1.62 (d, 15.0), 2.80 (d, 15.0)	35.8 t	1.57 m, 2.76 (d, 14.5)	35.7 t
D-3		90.9 s		90.9 s		91.0 s
D-4	4.37 (d, 10.5)	53.8 d	4.37 (d, 10.0)	53.9 d	4.37 (d, 10.0)	53.7 d
D-5	3.48 m	68.9 d	3.50 m	68.9 d	3.48 m	69.1 d
D-6	1.15 (d, 6.5)	17.0 q	1.15 (d, 6.0)	17.0 q	1.14 (d, 6.0)	17.0 q
D-7	1.59 s	25.3 q	1.58 s	25.3 q	1.56 s	25.3 q
D-8		157.4 s		157.4 s		157.5 s
D-9	3.70 s	52.7 q	3.75 s	52.7 q	3.70 s	52.7 q

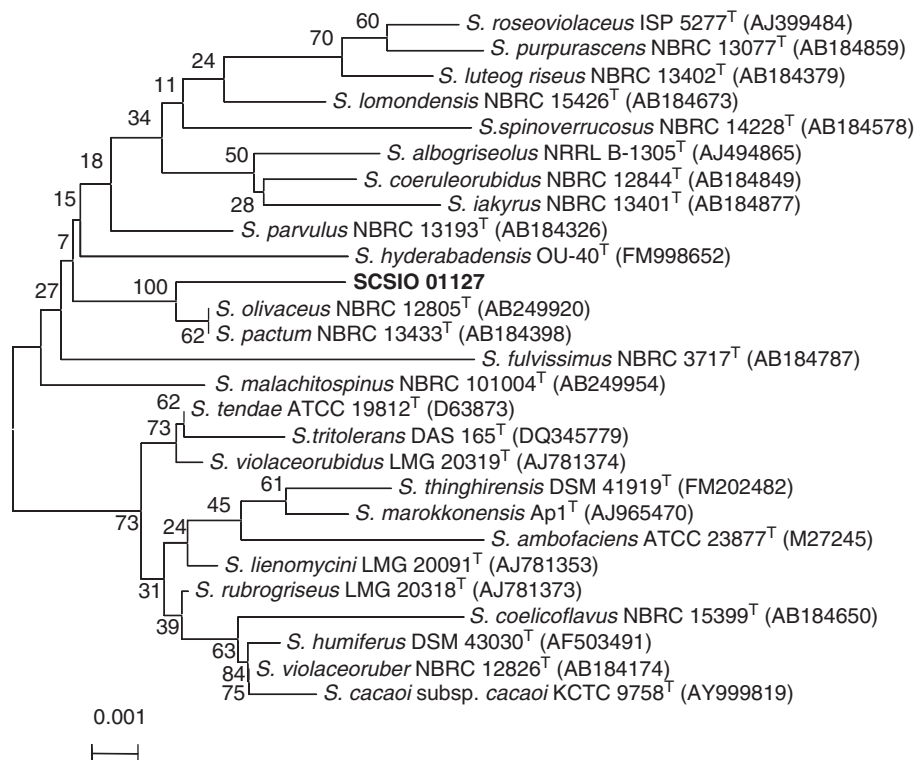


Figure 1 Phylogenetic dendrogram of the strain SCSIO 01127 and its closest relatives reconstructed by the neighbor-joining method on the basis of 16S rDNA gene sequences.

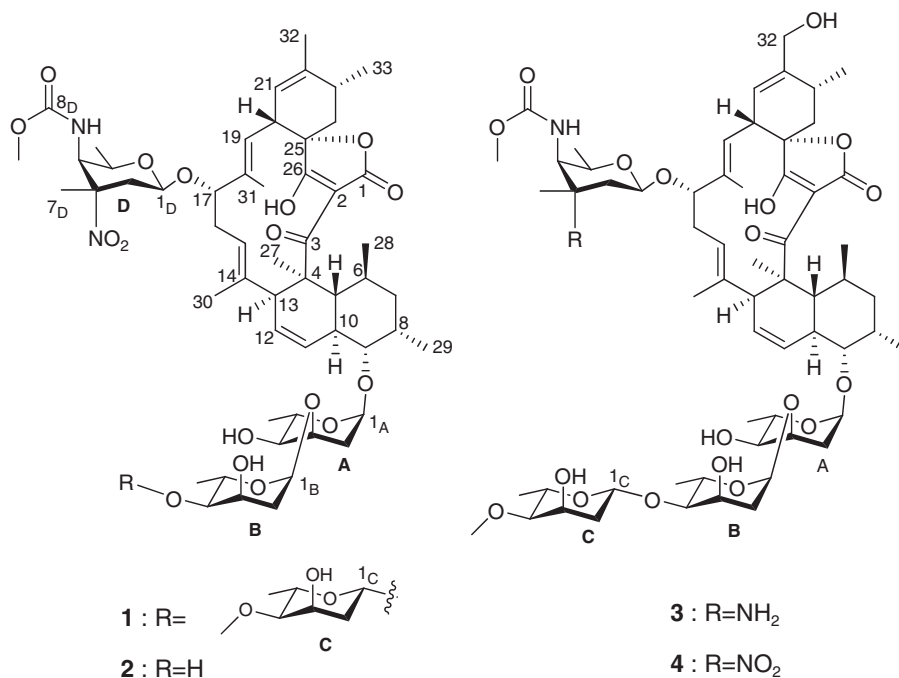


Figure 2 Chemical structures of lobophorins 1-4.

of **2** with **1**, the signals of 4-O-methyl-L-digitoxose moiety (sugar C, Figure 2) in **1** were absent in compound **2**. Consistent with the loss of this sugar moiety in **2**, 9.7 p.p.m. upfield shifting was observed for C-4_B (δ_C 72.5) in the sugar B moiety (Figure 2). In accordance with this

change occurring at C-4_B, the COSY correlation from H-4_B to H-3_B and H-5_B, and the HMBC correlation from H-6_B to C-4_B were observed (Figure 3). Based on these data, the structure of compound **2** was determined to be lobophorin F (Figure 2).

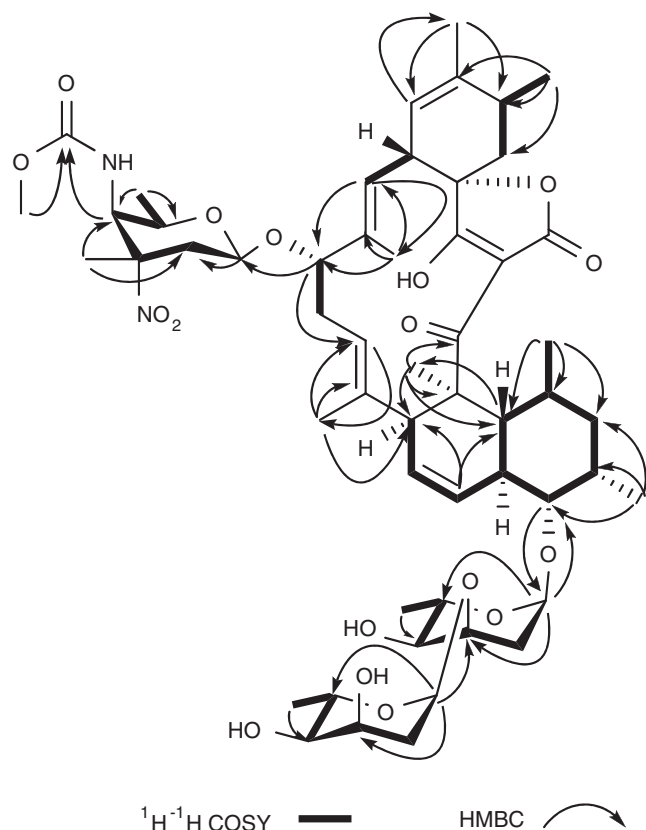


Figure 3 Selected key $^1\text{H}-^1\text{H}$ COSY and HMBC correlations of lobophorin F (2).

Table 2 Biological activities

Compounds	MIC ($\mu\text{g ml}^{-1}$)			IC ₅₀ (μM)		
	B. thuringensis SCSIO BT01	S. aureus	E. faecalis	SF-268	MCF-7	NCI-H460
		ATCC 29213	ATCC 29212			
1	8	32	128	ND ^a	ND ^a	ND ^a
2	2	8	8	6.82	2.93	3.16
3	8	>128	>128	NA ^b	>100	NA ^b
4	2	>128	32	18.3	5.84	26.6

^aNot tested.

^bNo activity observed.

Biological activity

Antibacterial activities of lobophorins (1–4) were evaluated against *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *B. thuringensis* SCSIO BT01 (Table 2). All four compounds exhibited activities against *B. thuringensis* SCSIO BT01 with MIC values of 8, 2, 8 and $2 \mu\text{g ml}^{-1}$, respectively. Compounds 1, 3 and 4 showed no activities or weak activities against *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213 (Table 2). In contrast, compound 2 (lobophorin F) displayed antibacterial activities against these two strains with MIC values of $8 \mu\text{g ml}^{-1}$. Compounds 2–4 were also assayed for *in vitro* cytotoxic activities against three human tumor cell lines: SF-268, MCF-7 and NCI-H460. Compound 2 showed overall better cytotoxic activities against these three tumor cell lines than 4, (Table 2) with almost ninefold improvement against NCI-H460 (3.16 and $26.6 \mu\text{M}$ for 2 and 4, respectively). However, no cytotoxicities were observed for compound 3 (lobophorin A) for all assayed three cell lines ($>100 \mu\text{M}$).

The spirotetronate antibiotics comprise of a class of antibacterial and antitumor natural products, such as antlermicin,¹³ chlorothricin,¹⁴ kijanimicin,¹⁵ decatromicins,¹⁶ saccharocarcins,¹⁷ tetrocarcins¹⁸ and versipelostatins.¹⁹ A pair of spirotetronate antibiotics lobophorins A (3) and B (4), previously isolated from an alga-associated acintobacterium, were shown to exhibit anti-inflammatory but no antimicrobial activities.¹⁰ Very recently, two C-8 stereoisomers of 3 and 4, named lobophorins C and D, were isolated from a marine sponge-related *Streptomyces* strain and were shown to have selective cytotoxicities against different cell lines.²⁰ Interestingly, our study reveals that the absence of the C-32 hydroxyl group in lobophorins E (1) and F (2), when compared with compound 4 ($>128 \mu\text{g ml}^{-1}$), significantly enhances their antimicrobial properties against *S. aureus* ATCC 29213: >16 -fold improvement with 2 ($8 \mu\text{g ml}^{-1}$). In comparison with the MIC values of 1 and 2, and the cytotoxicities of 2 and 4, (Table 2) one could also infer that the presence of the terminal sugar moiety (4-O-L-digitoxose, sugar C, Figure 2) is disadvantageous for the antimicrobial and antitumor property. The cytotoxicity of 4 is significantly better than that of 3 (Table 2), indicating that the presence of the nitro-sugar moiety is critical. These data also support that the change of sugar moieties can define, alter or mask natural product bioactivity.^{21,22} Finally, this study highlights the need of engineering the lobophorin biosynthetic pathway in *Streptomyces* sp. SCSIO 01127, to rationally design hydroxylation and glycosylations, for directed production of lobophorin F (2) or other novel analogs with improved bioactivities.

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