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BRIEF COMMUNICATION

Cytotoxic anthracycline and antibacterial tirandamycin analogues from a marine-derived *Streptomyces* sp. SCSIO 41399

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Abstract

Aranciamycin K (**1**) and isotirandamycin B (**2**) were isolated from a marine-derived *Streptomyces* sp. SCSIO 41399, along with the previously reported four anthracycline derivatives (**3**–**6**), and two known tirandamycin derivatives (**7** and **8**). Their structures including absolute configurations were determined by extensive analysis of their spectroscopic analysis and ECD calculation method. Most of the isolated compounds were tested for their cytotoxic, antibacterial, and antifungal activities. Compounds **2**, **7** and **8** displayed potent bacteriostatic effects against *Streptococcus agalactiae* with MIC values of 11.5, 5.9 and 5.7 μM, respectively. Besides, compounds **3**, **5** and **6** exhibited moderate in vitro cytotoxic activities against the K562 cell lines with IC_{50} values of 22.0 ± 0.20, 1.80 ± 0.01 and 12.1 ± 0.07 μM, respectively.

Anthracyclines, discovered in 1960s, are a very important class of anticancer compounds used for many years in the treatment of leukaemia, breast carcinoma and other solid tumours, in which the aglycon is a tetracyclic system with a 7,8,9,10-tetrahydro-tetracene-5,12-quinone skeleton [1, 2]. However, their clinical application has been limited by their toxic, dose-related side effects such as stomatitis, gastrointestinal disorders, and cumulative cardiotoxicity [3]. The naturally occurring tetramic acids are a structurally diverse class of compounds containing a 2,4-pyrrolidinedione ring system, in which tirandamycins are the more well-known members of this family [4, 5]. Tirandamycins have been demonstrated to exhibit extensive biological activities, especially for the activity against vancomycin-resistant *Enterococcus faecalis* [6, 7]. There is no doubt that it is an irresistible trend to find new antibiotics with improved activities and/or novel mechanisms of action.

During our continuing efforts to discover new anticancer and anti-infective natural products from marine microorganisms [8–10], a *Streptomyces* sp. (SCSIO 41399) was isolated from the *Porites* sp. coral collected from the Wenchang, Hainan province of China in May 2016 and selected for chemical study because its secondary metabolites showed antibacterial activity against *Streptococcus agalactiae*. Bioassay-guided fractionation of the culture extracts led to the isolation of one new anthracycline analogue, aranciamycin K (**1**), and one new tirandamycin analogue, isotirandamycin B (**2**), as well as the previously reported four anthracycline derivatives, γ-rhodomycinone (**3**) [2], β-rhodomycinone (**4**) [2], 262-6 (**5**) [11] and β-rhodomycin-II (**6**) [12], two known tirandamycin derivatives, tirandamycin A (**7**) [5, 6] and tirandamycin B (**8**) [5, 6]. Their structures including absolute configurations

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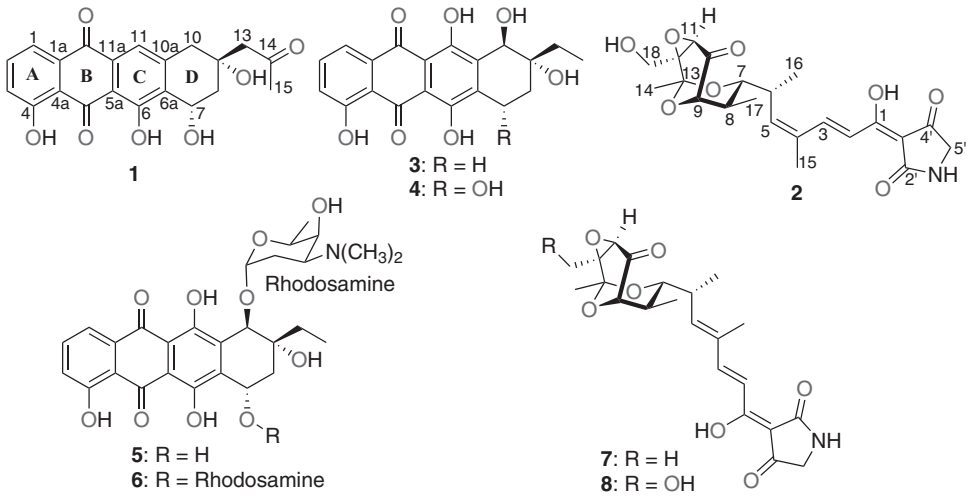

Fig. 1 Chemical structures of compounds **1–8**

were determined by extensive analysis of their spectroscopic analysis and ECD calculation method. Herein, details of the isolation, structural elucidation and cytotoxic, antibacterial and antifungal activities of compounds (**1–8**) are described.

The strain *Streptomyces* sp. SCSIO 41399 was incubated on a rotary shaker (180 rpm) at 28 °C for 7 days in 500 mL×150 Erlenmeyer flasks containing the liquid medium (200 mL/flask). The EtOAc extract (15.3 g) was fractionated by column chromatography (CC) over ODS, Sephadex LH-20 and high-performance liquid chromatography (HPLC), which led to the isolation of two new (**1** and **2**) and six known compounds (**3–8**) (Fig. 1).

Aranciamycin K (**1**) was obtained as yellow oils. Its molecular formula was determined to be $C_{21}H_{18}O_7$ with 13 degrees of unsaturation from HRESIMS at *m/z* 405.0950 $[M+Na]^+$ (calcd 405.0950) and 765.2170 $[2M+H]^+$ (calcd 765.2183). The relationships between specific proton and carbon signals in the ^1H and ^{13}C NMR data of compound **1** were established by DEPT and HMQC spectra. The ^1H NMR spectrum showed the presence of one singlet methyl [δ_H 2.19 (3H, s, H_3-15)], three methylenes [δ_H 2.13 (1H, d, $J = 13.5$ Hz, H-8a), 2.01 (1H, dd, $J = 13.5$, 3.9 Hz, H-8b) and 3.07 (1H, d, $J = 17.4$ Hz, H-10a), 3.01 (1H, d, $J = 17.4$ Hz, H-10b) and 2.72 (1H, d, $J = 14.1$ Hz, H-13a), 2.59 (1H, d, $J = 14.1$ Hz, H-13b)], one oxygenated methine [δ_H 5.04 (1H, s, H-7)] and four aromatic protons [δ_H 7.72 (1H, d, $J = 7.1$ Hz, H-1), 7.81 (1H, t, $J = 7.6$ Hz, H-2), 7.39 (1H, d, $J = 7.9$ Hz, H-3) and 7.46 (1H, s, H-11)]. The ^{13}C NMR spectrum, with the aid of the HSQC spectrum, provided 21 carbon resonance signals involving one methyl, three aliphatic methylenes, five methines, including four aromatic sp^2 ones, three ketone groups (δ_C 207.8, 191.9 and 181.3), one sp^3 quaternary carbon and eight sp^2 quaternary carbons. Comparison of UV−Vis and ^1H and ^{13}C NMR data with those of β-rhodomycinone (**4**) [2] revealed a high degree of similarity, indicating the same tetracyclic system with a 7,8,9,10-tetrahydro-tetracene-5,12-quinone skeleton. The main changes between **1** and **4** occurred on the cyclohexane moiety (D ring). In the ^{13}C NMR spectrum, the signals of one aliphatic methylene at δ_C 42.6 for C-10 and one acetone unit (δ_C 53.7, 207.8 and 32.6 for C-13/14/15, respectively) were observed in **1**, supporting the substitution of the oxygenated methine in the D ring and ethyl group in **4** by the aliphatic methylene and acetone unit in **1**, which was supported by the key HMBC correlations from H_2-10 to C-6a, C-9, C-10a, C-11 and C-13, and H_2-13 to C-8, C-9, C-10, C-14 and C-15. In addition, one singlet aromatic proton at δ_H 7.46 for H-11 was also observed in **1**, which was further supported by the key HMBC correlations from H-11 to C-5a, C-6a, C-10 and C-12 (Fig. 2). The NOESY correlation of H-7/H_2-13 indicated that 7-OH and 9-OH were on the same face (Fig. 3). To determine its absolute configuration, a computational modelling study was conducted using the Gaussian 03 programme package. The conformer of **1** was used as the input for the structural optimization by the density functional theory method at the B3LYP/6-31G(d) level in the Gaussian 03. The calculated ECD spectra of (7*S*,9*S*)-**1** and (7*R*,9*R*)-**1** were obtained by time-dependent density functional theory (TD-DFT) at the B3LYP/6-31G(d) level in MeOH. The calculated ECD spectrum of (7*S*,9*S*)-**1** was consistent with the experimental one (Fig. 4), confirming the absolute configuration of **1** to be 7*S* and 9*S*, respectively.

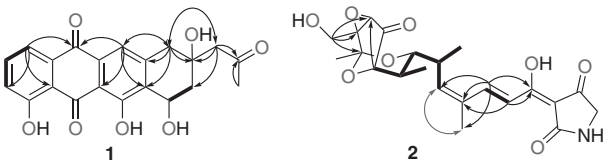

Fig. 2 Key ^1H–^1H COSY (bold), HMBC (arrows) correlations of **1** and **2**

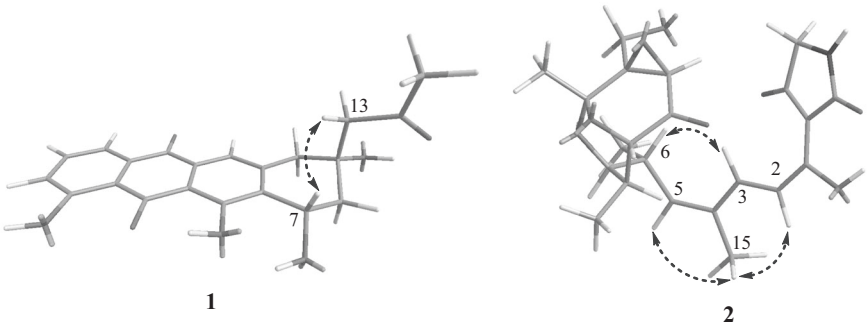

Fig. 3 Key NOESY correlations of compounds **1** and **2**

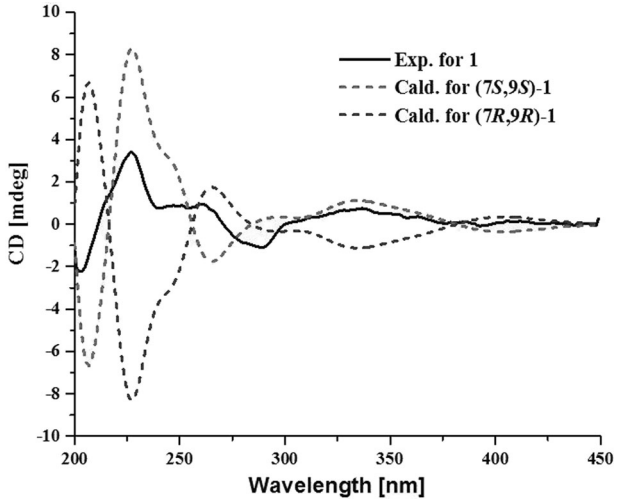

Fig. 4 Calculated and experimental ECD spectra of **1** in MeOH

Isotirandamycin B (**2**) was isolated as yellow oils with the molecular formula $C_{22}H_{27}NO_8$, as determined by HRESIMS at *m/z* 434.1810 $[M+H]^+$ (calcd 434.1815) and 456.1630 $[M+Na]^+$ (calcd 456.1634), indicating 10 degrees of unsaturation. Its ^1H NMR and ^{13}C NMR (DEPT) spectra include signals for two sp^2 quaternary carbons, two sp^3 quaternary carbons, three sp^2 methine carbons, five sp^3 methine carbons, two sp^3 methylene carbon, four methyls and one ketone group. The connectivity of the protons and C atoms was established by the ^1H, ^{13}C and HMQC spectra (Table 1). The general features of its NMR spectroscopic data closely resembled those of tirandamycin B (**8**) [5, 6]. Detailed comparison of NMR data of these two compounds (**2** and **8**) suggested that they had the same bicyclic keto and tetramic acid units. The significant differences in NMR spectra were observed in the signals for the polyene chain. These differences suggested that compound **2** and tirandamycin B (**8**) differed only in the geometry of the double bond in the polyene chain. The double bond between C-4 and C-5 of compound **2** possessed the (*Z*)-geometry, which was further deduced by the key NOESY correlation between H-5 (δ_H 6.04) and H_3-15 (δ_H 2.01) (Fig. 3). Additional NOESY correlations for the bicyclic keto moiety were in good agreement with the data for tirandamycins A and B (**7** and **8**) [5, 6]. Thus, the structure of **2** was suggested as the Δ^4 double bond isomerism of tirandamycin B (**8**), and named isotirandamycin B.

All the isolated compounds (**1**–**8**) were evaluated for their antibacterial and antifungal activities in 96-well microtiter plates using a modification of the broth microdilution method [13]. Isotirandamycin B (**2**), tirandamycin A (**7**) and tirandamycin B (**8**) displayed potent bacteriostatic effects against *S. agalactiae*, with MIC values of 5.0, 2.5 and 2.5 μg/mL, respectively. In addition, anthracycline analogues, 262-6 (**5**) and β-rhodomycin-II (**6**) showed weak antibacterial activities against *S. aureus* and *S. agalactiae*, with MIC values of 20.0/20.0, 40.0/20.0 μg/mL, respectively (Table 2). However, none of the compounds exhibited antifungal activities against five phytopathogenic fungi *C. gloeosporioides*, *C. asianum*, *C. acutatum*, *F. oxysporum* and *P. oryza*, respectively. Due to the paucity of material, most of the isolated metabolites, except for compound **1**, were evaluated for their cytotoxic activities against the K562 and BEL-7402 cell lines using the CCK-8 method as described previously [10]. Among them, compounds **3**, **5** and **6** exhibited moderate in vitro cytotoxic activities against the K562 cell lines with IC_{50} values of 22.0 ± 0.20, 1.80 ± 0.01 and 12.1 ± 0.07 μM (IC_{50} 0.21 ± 0.20 μM for Paclitaxel), respectively, while none of the tested compounds (**2**–**8**) exhibited cytotoxic activities ($IC_{50} \geq 30.0$ μM) against the BEL-7402 cell lines (IC_{50} 0.64 ± 0.20 μM for Paclitaxel).

In summary, to discover the structurally novel anticancer and anti-infective natural products from marine microorganisms originating from the South China Sea, one new anthracycline analogue, aranciamycin K (**1**), and one new tirandamycin analogue, isotirandamycin B (**2**), as well as the previously reported four anthracycline derivatives (**3**–**6**) and two known tirandamycin derivatives (**7** and **8**) were isolated from a marine-derived *Streptomyces* sp. SCSIO 41399. Compounds **3**, **5** and **6** exhibited moderate in vitro cytotoxic activities against the K562 cell lines. Besides, compounds **2**, **7** and **8** showed potent antibacterial effects against *S. agalactiae*, which might be used as candidates for the development of antibacterial agents.

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

Position	1[a]		2[b]	
	δ_C mult	δ_H (J in Hz)	δ_C mult	δ_H (J in Hz)
1	119.3, CH	7.72, d (7.1)	175.7, C	
1a	133.4, C			
2	137.4, CH	7.81, t (7.6)	120.3, CH	7.28, d (15.5)
3	124.4, CH	7.39, d (7.9)	140.8, CH	7.92, d (15.5)
4	161.3, C		134.3, C	
4a	116.0, C			
5	191.9, C		142.0, CH	6.04, d (10.5)
5a	113.5, C			
6	161.0, C		34.7, CH	3.10, m
6a	132.9, C			
7	61.2, CH	5.04, s	78.3, CH	3.76, d (10.6)
8	40.0, CH_2	2.13, d (13.5); 2.01, dd (13.5, 3.9)	35.5, CH	1.92, m
9	69.8, C		80.1, CH	3.99, dd (11.2, 6.1)
10	42.6, CH_2	3.07, d (17.4); 3.01, d (17.4)	203.3, C	
10a	145.2, C			
11	120.2, CH	7.46, s	57.9, CH	3.59, s
11a	131.7, C			
12	181.3, C		61.0, C	
13	53.7, CH_2	2.72, d (14.1); 2.59, d (14.1)	97.2, C	
14	207.8, C		23.7, CH_3	1.51, s
15	32.6, CH_3	2.19, s	20.3, CH_3	2.01, s
16			18.2, CH_3	1.15, d (6.9)
17			11.5, CH_3	0.70, d (6.9)
18			58.3, CH_2	3.97, d (9.8); 3.89, d (9.8)
2′			*	
3′			*	
4′			*	
5′			52.3, CH_2	3.82, brs
9-OH		5.47, s		

[a] ^{1}H and ^{13}C NMR data of **1** recorded at 700 MHz and 175 MHz in DMSO-d_6, respectively

[b] ^{1}H and ^{13}C NMR data of **2** recorded at 500 MHz and 125 MHz in CD_3OD, respectively

*Not observed

Materials and methods

General experimental procedures

Optical rotations were acquired using a PerkinElmer MPC 500 (Waltham) polarimeter. UV spectra were recorded on a UV-2600 spectrometer (Shimadzu). ^{1}H, ^{13}C NMR, DEPT and 2D-NMR spectra were recorded on the Avance III HD 700 MHz or the Avance-500 MHz spectrometer (Bruker). HRESIMS and ESIMS spectra data were recorded on a MaXis quadrupole-time-of-flight mass spectrometer and an amaZon SL ion trap mass spectrometer (Bruker), respectively. Circular dichroism spectra were recorded with a Chirascan circular dichroism spectrometer (Applied Photophysics, Ltd). Thin-layer chromatography (TLC) and CC were performed on plates precoated with silica gel GF_{254} (10–40 μm), and over silica gel (200–300 mesh) (Qingdao Marine Chemical Factory) and Sephadex LH-20 (Amersham Biosciences, Sweden), respectively. Vacuum liquid chromatography (VLC) used silica gel H (Qingdao Marine Chemical Factory). All solvents used were of analytical grade (Tianjin Fuyu Chemical and Industry Factory). Semipreparative HPLC was performed using an ODS column (YMC-pack ODS-A, 10 × 250 mm, 5 μm, 4 mL/min).

Actinomycete material

The actinomycete strain SCSIO 41399 was isolated from the *Porites* sp. coral collected from the Wenchang (19.535603°N, 110.860762°E), Hainan province of China in 2016. The frozen sample was defrosted and washed with sterile distilled water. The washed sample (1 g) was ground with sterile distilled water (10 mL) and then diluted to 10^{-3} g/mL, 100 μL of which was dispersed across a Humic acid–vitamin (HV) agar plate supplemented with cycloheximide (50 μg/mL), nystatin (50 μg/mL) and nalidixic acid (20 μg/mL), and incubated at 28 °C for 21 days. A single colony was transferred to the HV Agar medium. This strain (SCSIO 41399) was identified as *Streptomyces* sp. by morphological characteristics and sequence analysis of 16S rRNA (GenBank accession no. MG912556). A reference culture was maintained in our laboratory at –80 °C. The producing strain was prepared on Humic acid–vitamin Agar slants and stored at 4 °C.

Table 2 Antibacterial activities of compounds **1**–**8** (MIC, μg/mL)

Strains	Compounds								
	1	2	3	4	5	6	7	8	Erythromycin
Staphylococcus aureus	> 50	> 50	> 50	> 50	20.0	40.0	> 50	> 50	2.5
Streptococcus agalactiae	> 50	5.0	> 50	> 50	20.0	20.0	2.5	2.5	5.0

Erythromycin as the positive control

Fermentation and extraction

The strain SCSIO 41399 was incubated on a rotary shaker (180 rpm) at 28 °C for 7 days in 500 mL × 150 conical flasks containing the liquid medium (200 mL/flask) composed of soluble starch (25 mL/L), soybean powder (20 g/L), $MgSO_4{\cdot}7H_2O$ (0.6 g/L), $CaCO_3$ (0.2 g/L) and sea salt (10 g/L) (adjusted pH to 7.0 before sterilization). The fermented whole broth (30 L) was filtered through a cheesecloth to separate into filtrate and mycelia. The filtrate was concentrated under vacuum to about a quarter of the original volume and then extracted 3 times with EtOAc, while the mycelia were extracted 3 times with acetone. The acetone solution was evaporated under reduced pressure to afford an aqueous solution. The aqueous solution was extracted 3 times with EtOAc to give another EtOAc solution. Both EtOAc solutions were combined and concentrated under reduced pressure to give a dark brown gum (15.3 g).

Purification

The EtOAc extract (15.3 g) was subjected to VLC on a C_{18} reversed-phase silica gel using step gradient elution with MeOH–H_2O (5–100%) to separate into eight fractions based on TLC properties. Fraction 4 (3.6 g) was separated into five subfractions (Frs.4-1–4-5) by Sephadex LH-20 (MeOH). Fraction 4-3 (930 mg) was directly divided into six parts (Frs.4-3-1–4-3-6) by HPLC (45% CH_3CN-H_2O). Then, Fraction 4-3-3 was separated by HPLC (32% CH_3CN-H_2O + 0.1% CF_3CO_2H) to yield **8** (16.3 mg, t_R 32.0 min) and **2** (4.0 mg, t_R 40.4 min), respectively. Fraction 4-3-6 was separated by HPLC (58% CH_3CN-H_2O + 0.1% CF_3CO_2H) to yield **7** (9.4 mg, t_R 13.1 min). Fraction 4-4 was separated by HPLC (35% CH_3CN-H_2O) to yield **1** (2.0 mg, t_R 24.7 min). Fraction 6 (2.4 g) was divided into four parts (Frs.6-1–6-4) by Sephadex LH-20 (MeOH). Fraction 6-1 was further purified by HPLC (35% CH_3CN-H_2O + 0.1% CF_3CO_2H) to yield **6** (21.8 mg, t_R 5.0 min), **5** (9.4 mg, t_R 8.6 min) and **4** (4.1 mg, t_R 26.5 min), respectively. Fraction 6-3 was separated by HPLC (40.5% CH_3CN-H_2O + 0.1% CF_3CO_2H) to yield **3** (4.5 mg, t_R 36.1 min).

Aranciamycin K (**1**): yellow oils; $[\alpha]^{25}_D$ + 26.9 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε): 227 (4.18), 258 (3.99), 430 (3.56) nm; CD (0.2 μg/mL, MeOH), λ_{max} ($\Delta\varepsilon$) 227 (+ 3.45), 291 (−1.09), and 337 (+ 0.86); ^{1}H NMR (DMSO-d_6, 700 MHz) and ^{13}C NMR (DMSO-d_6, 175 MHz) data, see Table 1; (+)-HRESIMS *m/z* 405.0950 $[M+Na]^+$ (calcd for $C_{21}H_{18}NaO_7$, 405.0950), 765.2170 $[2M+H]^+$ (calcd for $C_{42}H_{37}O_{14}$, 765.2183) and 787.1991 $[2M+Na]^+$ (calcd for $C_{42}H_{36}NaO_{14}$, 787.2003).

Isotirandamycin B (**2**): yellow oils; $[\alpha]^{25}_D$ −9.6 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε): 250 (3.95), 292 (4.05), 337 (4.17) nm; ^{1}H NMR (CD_3OD, 500 MHz) and ^{13}C NMR (CD_3OD, 125 MHz) data, see Table 1; (+)-HRESIMS *m/z* 434.1810 $[M+H]^+$ (calcd for $C_{22}H_{28}NO_8$, 434.1815) and 456.1630 $[M+Na]^+$ (calcd for $C_{22}H_{27}NNaO_8$, 456.1634).

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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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