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Romipeptides A and B, two new romidepsin derivatives isolated from *Chromobacterium violaceum* No.968 and their antitumor activities *in vitro*

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[ABSTRACT] Romipeptides A and B (**1** and **2**), two new romidepsin derivatives, and three known compounds, chromopeptide A (**3**), romidepsin (**4**) and valine-leucine dipeptide (**5**) were isolated from the fermentation broth of *Chromobacterium violaceum* No. 968. Their structures were elucidated by interpretation of their UV, HR-ESI-MS and NMR spectra. The absolute configuration of compound **1** and **2** were established by single crystal X-ray diffraction analysis. Compounds **1**–**5** were evaluated for their anti-proliferative activities against three human cancer cell lines, SW620, HL60, and A549. The results showed most of these compounds exhibited antitumor activities *in vitro*, in which compound **2** displayed potent cytotoxicity to SW620, HL60 and A549 cell lines, with IC_{50} of 12.5, 6.7 and 5.7 nmol·L^{-1}, respectively.

[KEY WORDS] *Chromobacterium violaceum*; Romidepsin derivatives; Cytotoxicity.

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Introduction

The bacteria belonging to the genus *Chromobacterium* produce a wide variety of antibiotics, such as aerocyanidin, arphamenine A and violacein [1]. *Chromobacterium violaceum* No. 968 is one of the most studied bacterium because of the production of romidepsin [2], which was approved by FDA for the treatment of Recurrent T Lymphocytic Carcinoma in 2009 [3] and Peripheral T Lymphocytic Carcinoma in 2011 [4] respectively. Romidepsin is a promising antitumor drug and may also be used for the treatment of HIV [5]. Inspired by these discoveries, a series of romidepsin derivatives, such as thailandepsins [6], spiruchostatins [7] and chromopeptide A [8], have been isolated and characterized.

A chemical investigation of the extract from a large-scale fermentation of the *Chromobacterium violaceum* No. 968 led to the isolation of two new romidepsin derivatives, romipeptides A and B (**1** and **2**), together with three known compounds chromopeptide A (**3**) and romidepsin (**4**) and valine-leucine dipeptide (**5**) (Fig. 1). Their isolation, structural elucidation and cytotoxicity are reported herein.

Results

Compound **1** was obtained as a colorless crystal, with the molecular formula of $C_{48}H_{72}O_{12}N_8S_4$ based on HR-ESI-MS, ^{1}H NMR and ^{13}C NMR data. Compared with the molecular formula ($C_{24}H_{36}O_6N_4S_2$) of compound **4**, compound **1** might be the dimer of compound **4**. The ^{13}C NMR and DEPT data of compound **1** (Table 1) revealed the presence of 24 carbon signals, including one quaternary carbon, five carbonyl carbons, five methyl carbons, four methylene carbons and nine methine carbons, which were identical to those of compound **4**. Based on above analysis, the structure of compound **1** might be symmetrical. The ^{13}C NMR signals of compound **1** (Table 1) were similar to those of compound **4**, except the signals for C-20 (C-20'), C-16 (C-16'), C-11 (C-11'), C-10 (C-10') and C-9 (C-9'), which related to disulfide bonds. By comparison of the ^{13}C NMR data of compounds **1** and **4**, chemical shift values for C-11 (C-11') and C-16 (C-16') were very different with δ_C 52.3 and δ_C 41.4 presented in compound **1**, while δ_C 56.6 and δ_C 35.2 presented in compound **4**, respectively. The carbon C-16 was directedly connected at the disulfide bond and the carbon C-11 was connected at C-16 in compound **4**. Based on the above analysis, the disulfide bonds of compound **1** might be formed between two molecules of compound **4**. The struc-

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ture of compound **1** was further deduced by comprehensive interpretation of its ^{1}H-^{1}H COSY and HMBC spectra (Fig. 2).

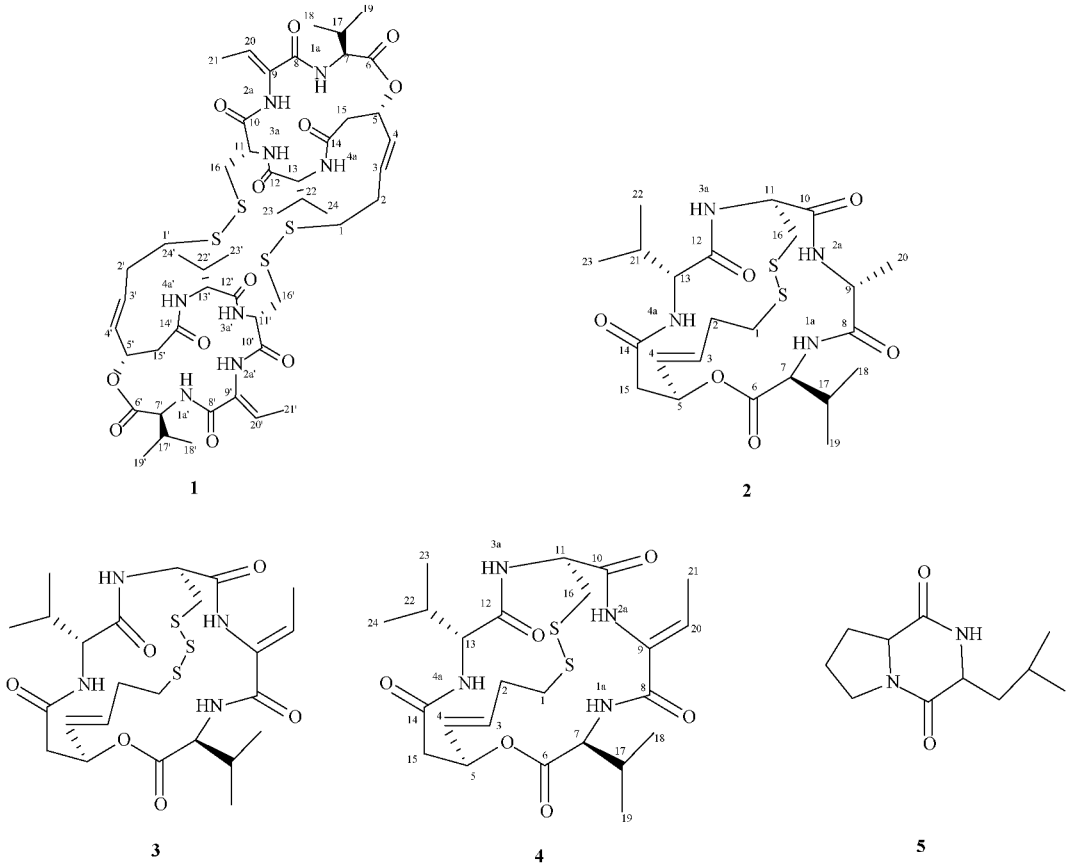

Fig. 1 Chemical structures of compounds 1–5

Table 1 ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) data for compound 1 (in DMSO-d_6)

Position	1				4
	δ_C, mult	δ_H (*J* in Hz)	HMBC	^{1}H-^{1}H COSY	δ_C, mult
1 (1')	37.2, CH_2	2.76–2.83, m	2 (2'), 3 (3')	H_2-2 (H_2-2')	37.8, CH_2
2 (2')	31.5, CH_2	2.38–2.43, m	1 (1'), 3 (3')	H_2-1 (H_2-1'), H-3 (H-3')	30.0, CH_2
3 (3')	128.9, CH	5.69, m	2 (2'), 4 (4')	H_2-2 (H_2-2'), H-4 (H-4')	129.3, CH
4 (4')	129.1, CH	5.73, m	3 (3'), 5 (5')	H-3 (H-3'), H-5 (H-5')	130.3, CH
5 (5')	70.5, CH	5.56, t (5.0)	4 (4'), 6 (6'), 15 (15')	H_2-15 (H_2-15'), H-4 (H-4')	70.7, CH
6 (6')	169.3, qC				169.0, qC
7 (7')	56.7, CH	4.54, dd (9.5 4.8)	6 (6'), 8 (8'), 17 (17'), 18 (18'), 19 (19')	H-17 (H-17'), H-1a (H-1a')	58.3, CH
8 (8')	162.7, qC				164.8, qC
9 (9')	128.8, qC				130.2, qC
10 (10')	168.9, qC				167.8, qC
11 (11')	52.3, CH	4.66, m	10 (10'), 14 (14'), 16 (16')	H_2-16 (H_2-16), H-3a (H-3a')	56.6, CH
12 (12')	170.2, qC				171.0, qC
13 (13')	60.2, CH	3.9, t (6.2)	12 (12'), 14 (14'), 22 (22'), 23 (23'), 24 (24')	H-22 (H-22), H-4a (H-4a')	61.7, CH
14 (14')	169.0, qC				171.6, qC
15 (15')	39.3, CH_2	2.57-2.67, m	4 (4'), 5 (5'), 14 (14')	H-5 (H-5')	37.7, CH_2
16 (16')	41.4, CH_2	2.94-3.11, m	10 (10'), 11 (11')	H-11 (H-11')	35.2, CH_2

Continued

Position	**1**[a]				**4**[a]
	δ_C, mult	δ_H (*J* in Hz)	HMBC	^{1}H-^{1}H COSY	δ_C, mult
17 (17')	31.0, CH	2.21, m	6 (6'), 7 (7'), 18 (18'), 19 (19')	H-7 (H-7'), H_3-18 (H_3-18'), H_3-19 (H_3-19')	30.6, CH
18 (18')	19.2, CH_3	0.83, d (6.8)	7 (7'), 17 (17'), 19 (19')	H-17 (H-17')	18.6, CH_3
19 (19')	17.3, CH_3	0.83, d (6.8)	7 (7'), 17 (17'), 18 (18')	H-17 (H-17')	18.5, CH_3
20 (20')	133.3, CH	6.76, m	8 (8'), 9 (9'), 21 (21')	H_3-21 (H_3-21'), H-2a (H-2a')	127.2, CH
21 (21')	13.5, CH_3	1.69, d (7.1)	8 (8'), 9 (9'), 20 (20')	H-20 (H-20'), H-2a (H-2a')	13.3, CH_3
22 (22')	29.2, CH	2.12, m	12 (12'), 13 (13'), 22 (22'), 23 (23')	H-13 (H-13'), H_3-23 (H_3-23'), H_3-24 (H_3-24')	28.5, CH
23 (23')	17.9, CH_3	0.89, d (6.8)	12 (12'), 22 (22'), 24 (24')	H-22 (H-22')	19.0, CH_3
24 (24')	19.0, CH_3	0.93, d (6.8)	13 (13'), 22 (22'), 23 (23')	H-22 (H-22')	18.9, CH_3
1a (1a')		6.44, d (9.5)	7 (7'), 8 (8')	H-7 (H-7')	
2a (2a')		9.71, s		H-21 (H-21')	
3a (3a')		7.09, s		H-11 (H-11')	
4a (4a')		7.77, d (6.6)	14 (14')	H-13 (H-13')	

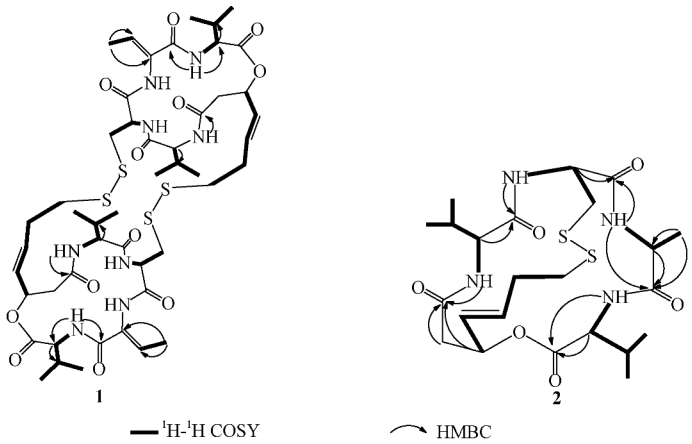

Fig. 2 key H^1-H^1 COSY and HMBC correlations of 1 and 2

To confirm the assumed structure and determine its absolute configuration, a suitable crystal of compound **1**, obtained from MeOH, was subjected to single crystal X-ray diffraction analysis [9-10]. On the basis of the above data, compound **1** was formed from two molecules of compound **4** through intermolecular disulfide bonds**.** The structure of compound **1** was assigned (Fig. 1) and the compound was named romipeptide A.

Compound **2** was obtained as a white powder with the molecular formula of $C_{23}H_{36}O_6N_4S_2$ based on HR-ESI-MS, which was one less carbon than that ($C_{24}H_{36}O_6N_4S_2$) of compound **4**. The ^{13}C NMR and DEPT data of compound **2** (Table 2) showed the presence of 23 carbon signals, including five methyl carbons, four methylene carbons, nine methine carbons and five carbonyl carbons. By the comparison of ^{13}C-NMR spectra of compounds **2** and **4** (Table 2), it was found that the tri-substituted double bond of compound **4**, including a quaternary carbon C-9 (δ_C 130.5) and an unsaturated methine C-20 (δ_C 128.6), disappeared in compound **2**, while, an additional saturated methine carbon C-9 (δ_C 50.9) and a methyl crbon C-20 (δ_C 15.0) appeared in compound **2**. The HMBC spectrum of compound **2** (Fig. 2) indicated the correlation from the saturated methine proton H-9 (δ_H 3.85) to C-8 (δ_C 170.2) and C-10 (δ_C 169.5) and methyl protons H_3-20 (δ_H 1.51) to C-9 (δ_C 50.9) and C-8 (δ_C 170.2), suggesting that the methyl carbon C-20 (δ_C 15.0) was connected at C-9 (δ_C 50.9). This partial structure was confirmed by the ^{1}H-^{1}H COSY correlation from H_3-20 (δ_H 1.51) to H-9 (δ_H 3.85) in compound **2**. Based on above analysis, the chemical structure of compound **2** was very similar to that of compound **4**, which the main difference between them was that the vinyl methyl group in compound **4** was replaced by a methyl group in compound **2**.

To confirm the absolute configuration, a suitable crystal of compound **2**, obtained from acetone, was subjected to single crystal X-ray diffraction analysis analysis. Thus, the structure of compound **2** was confidently assigned (Fig. 1) and the compound was named romipeptide B.

Table 2 ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) data for compound 2 (in $CDCl_3$)

Position	2				4
	δ_C, mult	δ_H (*J* in Hz)	HMBC	^{1}H-^{1}H COSY	δ_C, mult
1	38.1, CH_2	3.01, m; 3.15, m	2, 3	H_2-2	38.2, CH_2
2	30.9, CH_2	2.6, m; 2.68, m	1, 3	H_2-1, H-3	30.5, CH_2
3	129.8, CH	5.72, m	2, 4	H_2-2, H-4	130.0, CH
4	131.7, CH	5.73, m	3, 5	H-3, H-5	131.2, CH
5	69.5, CH	5.73, m	4, 6, 15	H_2-15, H-4	69.8, CH
6	169.9, qC				169.2, qC
7	57.1, CH	4.78, dd (8.5, 3.6)	6, 8, 17, 18, 19	H-17, H-1'	58.1, CH
8	170.2, qC				165.1, qC
9	50.9, CH	3.85, p (6.8)	8, 10, 20	H_3-20, H-2'	130.5, qC
10	169.5, qC				168.6, qC
11	55.7, CH	4.66, ddd (11.7, 7.1, 4.3)	10, 12, 16	H-3', H_2-16,	56.2, CH
12	172.4, qC				172.3, qC
13	61.9, CH	4.09, dd (6.8, 5.2)	12, 14, 21, 22, 23	H-21, H-4'	62.4, CH
14	169.6, qC				170.4, qC
15	38.2, CH_2	2.69, m, 2.89, dd (13.3, 7.1)	4, 5, 14	H-5	38.1, CH_2
16	33.6, CH_2	3.02, m, 3.31, dd (16.0, 11.8)	10, 11	H-11	34.1, CH_2
17	31.9, CH	2.41, dd (6.9, 3.6)	6, 7, 18, 19	H-7, H_3-18, H_3-19	32.3, CH
18	19.0, CH_3	0.97, d (3.8)	7, 17, 19	H-17	18.5, CH_3
19	17.8, CH_3	0.99, d (3.8)	7, 17, 18	H-17	18.4, CH_3
20	15.0, CH_3	1.51, d (6.9)	8, 9	H-9	128.6, CH
21	29.2, CH	2.21, m	8, 12, 13, 22, 23	H-13, H_3-22, H_3-23	13.2, CH_3
22	19.7, CH_3	1.11, d (1.5)	13, 21, 23	H-21	29.2, CH
23	19.6, CH_3	1.09, d (1.5)	13, 21, 22	H-21	19.8, CH_3
24					19.5, CH_3
1a		7.07, d (8.5)	7, 8	H-7	
2a		7.54, d (6.6)	8, 9, 10	H-9	
3a		7.67, d (7.1)	11, 12, 16	H-11	
4a		6.36, d (5.3)	12, 13, 14, 21	H-13	

The other compounds **3**, **4** and **5**, isolated from the crude extract were identified as chromopeptide A (**3**) [8] and romidepsin (**4**) [11] and valine-leucine dipeptide (**5**) [12], respectively, by comparison of their NMR and MS data with those reported.

Compounds **1**–**5** were tested for cytotoxicity against three human tumor cell lines, SW620, HL-60 and A549, using the MTT assay [13]. Compound **2** showed similar cytotoxic against SW620, HL60 and A549 cells (IC_{50} 12.5, 6.7 and 5.7 nmol·L^{-1}, respectively) compared with that of romidepsin (IC_{50} 7.3, 4.9 and 5.3 nmol·L^{-1}, respectively) (Table 3).

Table 3 Cytotoxic activities of compounds 1, 2, 3, 4 and 5 (*n* = 3)

Cells	IC_{50} (nmol·L^{-1})					
	1	**2**	**3**	**4**	**5**	Cisplatin
SW620	42.5 ± 5.3	12.5 ± 2.9	18.6 ± 5.0	7.3 ± 3.3	(6.4 ± 2.8) × 10^3	(2.3 ± 0.8) × 10^3
HL-60	21.8 ± 8.7	6.7 ± 3.4	12.7 ± 5.6	4.9 ± 1.8	(6.2 ± 2.3) × 10^3	(5.4 ± 1.3) × 10^3
A549	40.6 ± 3.4	5.7 ± 2.8	9.6 ± 4.1	5.3 ± 0.8	(7.7 ± 2.4) × 10^3	(1.4 ± 0.5) × 10^3

In this study, chemical investigation of *Chromobacterium violaceum* No. 968 has led to isolation of two new romidepsin derivatives, romipeptides B and C (**1** and **2**), which may be promising for the development of effective drugs for various cancers [6-7].

Experimental

General procedures

1D and 2D NMR spectra were obtained on Bruker Avance-400 FT NMR spectrometer (400 MHz) (Bruker BioSpin GmBH, Rheinstetten, Germany) with TMS as an internal standard. Chemical shifts (δ) were expressed in ppm with reference to solvent signals. HR-ESI-MS was recorded on a Waters Alliance (2695/2487) Q-Tof micro (Waters Corp., Milford, MA, USA). Single crystal X-ray diffraction (SCXRD) was recorded on a Bruker SMART APEX-II (Bruker BioSpin GmBH, Rheinstetten, Germany). Column chromatography was performed on silica gel (200−300/300−400 mesh, Qingdao Marine Chemical Co., Ltd., Qingdao, China). High-performance liquid chromatography (HPLC) was employed using Elite P270 pumps and Elite UV 230 + detector (Elite Analytical Instruments Co., Ltd., Dalian China) coupled with an Agela C_{18} preparative column (250 mm × 30 mm, 10 μm, Venusil ASB C_{18}, Agela Technologies Co., Ltd., Tianjin, China). Fermentation was performed in FUS-5L fermentor (National center of Bio-Engineering & Technology, Shanghai, China).

Bacterial material and fermentation

The strain used in this experiment was *Chromobacterium violaceum* No. 968 (No. FERM BP-1968, From IPOD[a]) [14-15]. The bacterial strain was cultured on nutrient agar (Bio-way technology Corp., Shanghai, China) at 30 °C for 24 h. The seeds from the above was inoculated into 250 mL erlenmeyer flask containing 30 mL sterile seed liquid medium containing 2.0% peptone and 2.0% glucose, PH 6.0, and cultured on a rotary shaker (250 r·min^{-1}) at 30 °C for 16 h. Fermentation was performed in 5 L fermentor containing 3 L culture medium (3.0% glucose, 1.0% starch, 2.0% mannitol, 1.0% hydrolysis casein, 0.8% beef extract, 0.6% KH_2PO_4, 0.2% cysteine, 0.4% soybean oil and 0.2% $CaCO_3$, PH 5.5). The fermentor was inoculated with 2.0% of the seed culture and maintained on a 520 rpm rotary shaker at 25 °C for 52 h.

Isolation and purification

After the fermentation was completed, the PH of the fermentation broth was adjusted to 3.0 with hydrochloric acid, then the fermentation broth was extracted with EtOAc (5 L) and the organic layer was evaporated to dryness (14.1 g). The extract (14.1 g) was separated on a silica gel column with a gradient solvent system of cyclohexane–EtOAc (5 : 5 to 1 : 9, *V*/*V*) to give three fractions (Frs. 1–3). Fr. 1 (4.6 g) was purified on a silica gel column with a gradient solvent system of cyclohexane–isopropanol (10 : 0 to 8 : 2, *V*/*V*) to yield compounds **3** (0.03 g), **4** (1.18 g) and **5** (0.03 g). Fr. 2 (0.25 g) was purified on a preparative RP HPLC using a solvent system of CH_3CN–H_2O (4 : 6, *V*/*V*) to yield crude compound **1** (0.15 g). Crude compound **1** (0.15 g) was dissolved in 4 mL methanol and kept in 4 °C for 72 h, then crystals of compound **1** (0.05 g) were obtained. Fr. 3 (0.21 g) was purified on a silica gel column with a gradient solvent system of cyclohexane–EtOAc (3 : 7 to 10 : 0, *V*/*V*) to afford compound **2** (0.03 g).

Romipeptide A (**1**): colorless crystal. $[\alpha]_D^{20}$ −53.9 (*c* 0.03, $CHCl_3$). UV (MeOH) λ_{max} nm (ε): end absorption. IR (KBr) υ_{max} : 3385, 3252, 2967, 2932, 1740, 1655, 1518, 1468, 1441, 1393, 1373, 1350, 1333, 1261, 1180, 1157, 1096, 989 cm^{-1}. MP: 190−198 °C. ^{1}H NMR, ^{13}C NMR and HMBC and ^{1}H-^{1}H COSY, see Table 1. HR-ESI-MS *m/z* 1103.4020 $[M + Na]^+$ (Calcd. for $C_{48}H_{72}O_{12}N_8S_4Na$, 1103.4050).

Romipeptide B (**2**): colorless crystal. $[\alpha]_D^{20}$ +15.7(*c* 0.03, $CHCl_3$). UV (MeOH) λ_{max} nm (ε): end absorption. IR (KBr) υ_{max} : 3329, 3293, 2961, 2932, 2876, 1738, 1690, 1655, 1530, 1468, 1454, 1395, 1364, 1335, 1256, 1188, 1161, 1053, 1018, 970 cm^{-1}. MP: 244−248 °C. ^{1}H NMR, ^{13}C NMR and HMBC and ^{1}H-^{1}H COSY, see Table 2. HR-ESI-MS *m/z* 529.2142 $[M + H]^+$ (Calcd. for $C_{23}H_{36}O_6N_4S_4$, 529.2155).

Cytotoxicity

The cytotoxicity of compounds **1**−**5** were tested *in vitro* using human cancer cell lines including HL60 (acute promyelocytic leukemia), SW620 (colonic carcinoma) and A549 (lung adenocarcinoma). The MTT method was used for the bioassays as described in the literature [2]. Cisplatin was used as a positive control [16].

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