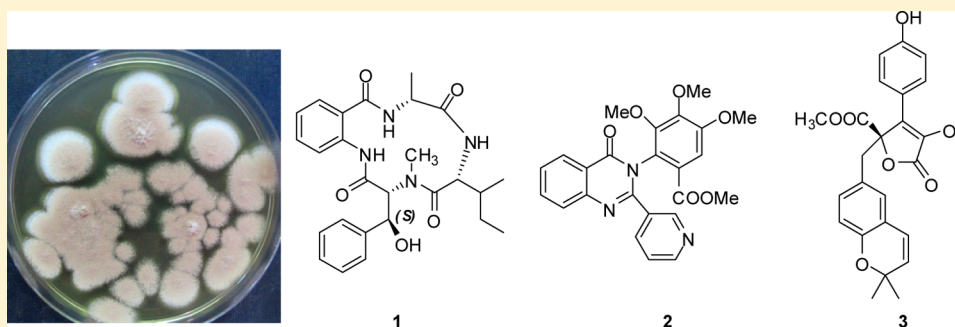


Asperterrestide A, a Cytotoxic Cyclic Tetrapeptide from the Marine-Derived Fungus *Aspergillus terreus* SCSGAF0162Fei He,[†] Jie Bao,[†] Xiao-Yong Zhang,[†] Zheng-Chao Tu,[‡] Yi-Ming Shi,[§] and Shu-Hua Qi*,[†][†]Key Laboratory of Marine Bio-resources Sustainable Utilization/RNAM Center for Marine Microbiology/Guangdong Key Laboratory of Marine Material Medical, South China Sea Institute of Oceanology, Chinese Academy of Sciences, 164 West Xingang Road, Guangzhou 510301, People's Republic of China[‡]Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, 190 Kaiyuan Road, Guangzhou 510530, People's Republic of China[§]State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, People's Republic of China

S Supporting Information



ABSTRACT: A new cytotoxic and antiviral cyclic tetrapeptide, asperterrestide A (**1**), a new alkaloid, terremide C (**2**), and a new aromatic butenolide, aspernolide E (**3**), together with 10 known compounds were isolated from the fermentation broth of the marine-derived fungus *Aspergillus terreus* SCSGAF0162. Their structures were elucidated by spectroscopic analysis, and the absolute configuration of **1** was determined by the Mosher ester technique and analysis of the acid hydrolysates using a chiral-phase HPLC column. Compound **1** contains a rare 3-OH-N-CH₃-Phe residue and showed cytotoxicity against U937 and MOLT4 human carcinoma cell lines and inhibitory effects on influenza virus strains H1N1 and H3N2.

Marine microorganisms have proved to be an important source of pharmacologically active metabolites, and a growing number of marine-derived fungi have been reported to produce metabolites with unique structures and interesting biological activities.¹ The genus *Aspergillus* (Moniliaceae), with over 180 species, has attracted considerable attention as a rich source of alkaloids, terpenoids, xanthenes, and polyketides, some of which showed antifungal, antibacterial, antifouling, and cytotoxic activities.^{2–4} *Aspergillus terreus* is commonly isolated from soil with worldwide distribution and has been found to produce a number of bioactive compounds, such as terreineol,⁵ terrain,⁶ aspulvinone,⁷ butyrolactone I,⁸ and terreic acid.⁹ With the aim of searching for novel bioactive natural compounds from marine fungi, we investigated the chemical constituents of a fermentation broth of the marine-derived fungal strain *A. terreus* SCSGAF0162. Three new compounds, the cyclic tetrapeptide asperterrestide A (**1**), the alkaloid terremide C (**2**), and the aromatic butenolide aspernolide E (**3**), together with 10 known compounds, methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate (**4**),¹⁰ butyrolactone I,⁸ butyrolactone III,¹¹ butyrolactone II,⁸ 4-(4-hydroxyphenyl)-5-(4-hydroxyphenylmethyl)-2-hydroxyfuran-2-one,¹² territrem

C,¹³ arisugasin H,¹⁴ arisugasin D,¹⁴ territrem B,¹³ and territrem A,¹³ were isolated. Compound **1** was tested for its cytotoxicity toward human carcinoma U937, K562, BGC-823, MOLT-4, MCF-7, and A549 cell lines and antiviral activity toward two influenza virus strains.

Asperterrestide A (**1**) was obtained as a yellowish powder. It was assigned a molecular formula of C₂₆H₃₂N₄O₅ on the basis of its HRESIMS data. Analysis of the ¹H and ¹³C NMR spectra (Table 1) revealed the presence of three amide N-H protons (δ_{H} 6.48, 7.18, and 9.17), four methyl groups (including one N-methyl), one methylene group, two phenyl rings, five methines (four of which were bound to heteroatoms), and four carbonyl carbons. Interpretation of the ¹H, ¹³C, and 2D NMR data of **1** suggested a peptidic nature for the molecule. By analysis of the COSY and HMBC spectra of **1**, the aromatic protons at δ_{H} 7.36 (1H, d, *J* = 8.0 Hz), 7.15 (1H, dd, *J* = 7.5, 8.0 Hz), 7.48 (1H, dd, *J* = 7.5, 8.0 Hz), and 8.17 (1H, d, *J* = 8.0 Hz) represented an *ortho*-disubstituted benzene ring. HMBC correlations from

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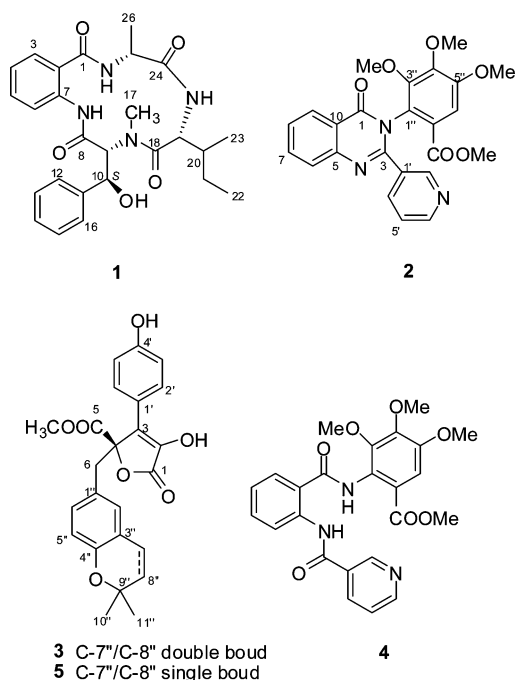


Table 1. NMR Data for **1** (500 MHz for ^1H and 125 MHz for ^{13}C NMR in CDCl_3)

unit	position	δ_{C} , type	δ_{H} , mult (J in Hz)	HMBC ^b
ABA	1	170.3, C		
	2	126.7, C		
	3	125.6, CH	7.36, d (8.0)	1, 5, 7
	4	124.5, CH	7.15, dd (7.5, 8.0)	2, 6
	5	131.5, CH	7.48, dd (7.5, 8.0)	3, 6, 7
	6	123.5, CH	8.17, d (8.0)	2, 4, 7
	7	135.1, C		
3-OH-N-Me-Phe	NH		9.17, s	2, 6
	8	169.1, C		
	9	60.9, CH	5.76, d (10.0)	8, 10, 11, 17
	10	71.4, CH	5.15, d (10.0)	8, 9, 11, 12
	11	138.7, C		
	12/16	127.5, CH	7.39 ^a	10, 13
	13/15	128.5, CH	7.33 ^a	
Ile	14	127.6, CH ^a	7.26 ^a	
	17	31.4, CH ₃	2.75, s	9, 18
	18	172.5, C		
	19	53.9, CH	4.31, dd (10.0, 10.5)	20, 21, 23
	20	36.1, CH	1.75, m	
	21	24.7, CH ₂	0.30, m	19, 20, 22, 23
	22	10.8, CH ₃	0.54, dd (7.0, 7.5)	20, 21
Ala	23	14.5, CH ₃	0.79, d (6.5)	19, 20, 21
	NH		7.18, d (9.5)	
	24	171.3, C		
	25	50.1, CH	4.52, m	24, 26
	26	14.8, CH ₃	1.43, d (7.0)	24, 25
	NH		6.48, d (8.0)	25, 26

^aOverlapped signals. ^bHMBC correlations are from proton(s) started to the indicated carbon.

H-3 (δ_{H} 7.36) to C-1 (δ_{C} 170.3) and from N-H (δ_{H} 9.17) to C-7 (δ_{C} 135.1) led to the identification of an anthranilic acid (ABA) unit. Similarly, three other amino acid units including 3-OH-N-Me-phenylalanine (3-OH-N-Me-Phe), isoleucine (Ile),

and alanine (Ala) were completely assigned. Specifically, the loss of Ala (m/z 71) and Ile (m/z 113) fragments was deduced from the ESIMS² spectrum (Supporting Information). Upon extensive analysis of these data, asperterrestide A (**1**) was assigned as a cyclic tetrapeptide containing ABA, 3-OH-N-Me-Phe, Ile, and Ala.

The amino acid sequence of **1** was deduced from NOESY correlations between α -protons and neighboring residue NH groups, with support from HMBC correlations. The N-H proton of ABA (δ_{H} 9.17) showed an HMBC correlation with the carbonyl carbon of C-8, indicating that it was acylated by 3-OH-N-Me-Phe, and this connection was also confirmed by the NOESY correlation between the N-H of ABA and H-9 (Figure 1). An HMBC correlation from H₃-17 to C-18 supported the

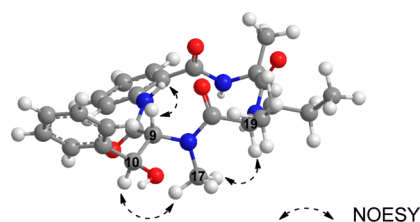


Figure 1. Key NOESY correlations of compound **1**.

connection of Ile and 3-OH-N-Me-Phe. HMBC correlations from the N-H proton (δ_{H} 7.18) and H-19 of Ile to C-24, together with the NOESY correlation between H-25 and the N-H proton of Ile, supported the connection of the Ile and Ala residues. The HMBC correlation from the N-H proton (δ_{H} 6.48) of Ala to C-1 supported the connection of Ala and ABA residues. Therefore, the complete sequence of **1** was deduced.

The large coupling constant (J = 10.0 Hz) between H-9 and H-10 of the β -hydroxy-N-Me-phenylalanine residue suggested a *syn* relative configuration for the two protons.¹⁵ A molecular modeling experiment and the observation of NOE correlations of H₃-17 with H-10 and of H-9 with N-H (ABA) in the NOESY spectrum of **1** (Figure 1) further confirmed this deduction. The geometries for modeling were obtained in Chem3D 11.0 and then optimized at the AM1 level using Gaussian 09.¹⁶ The absolute configurations of the Ala and Ile residues were determined by analysis of acid hydrolysates on a chiral-phase HPLC column^{17,18} and Marfey's methods.^{19,20} HPLC analyses of the mixture of hydrolysates and authentic samples (co-injection) confirmed D-Ala in **1**. Through a chiral-phase HPLC analysis, the D-Ile and D-allo-Ile residues could not be differentiated because the retention times of these two compounds were identical. D-Ile and D-allo-Ile were not resolved even using Marfey's method.²¹ The absolute configuration of C-10 in **1** was determined using the modified Mosher's ester method in an NMR tube.²² Compound **1** was treated separately with (R)-(-)- and (S)-(+)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) in pyridine-*d*₅ in an NMR tube to yield the (S)- and (R)-MTPA ester derivatives **1a** and **1b**, respectively. The neighboring signals of H-10 were clearly different in the diastereomeric MTPA esters (**1a** and **1b**), and the observed chemical shift differences ($\Delta\delta_{\text{S-R}}$, Figure 2) unambiguously indicated the absolute configuration of C-10 of **1** to be *S*. Consequently, the structure of **1** was elucidated as cyclo-[ABA-D-Ala-Ile-3(*S*)-OH-N-Me-Phe].

Terremide C (**2**) gave an HRESIMS ion peak at m/z 448.1510 [$\text{M} + \text{H}$]⁺, corresponding to the molecular formula

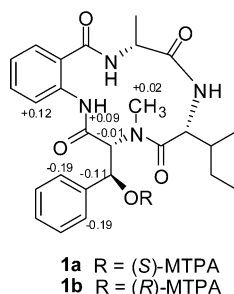


Figure 2. $\Delta\delta$ ($\delta_S - \delta_R$) values in ppm for MTPA esters of 1.

$C_{24}H_{21}N_3O_6$, which required 16 degrees of unsaturation. The UV spectrum displayed absorptions at λ_{max} 225 and 268 nm. The 1H and ^{13}C NMR spectra (Table 2) were quite similar to

Table 2. 1H (500 MHz) and ^{13}C (125 MHz) NMR Data for Compounds 2 and 3 in $CDCl_3$

position	2 ^b			3 ^c		
	δ_C , type	δ_H , mult (J in Hz)		δ_C , type	δ_H , mult (J in Hz)	
1	162.5, C			d		
2				d		
3	131.5, C			127.8, C		
4				86.7, C		
5	148.0, C			169.7, C		
6	128.2, CH	7.84 ^a		38.6, CH ₂	3.45, d (15)	
					3.55, d (15)	
7	134.8, CH	7.84 ^a				
8	127.3, CH	7.56, m				
9	127.8, CH	8.35, d (8.0)				
10	121.0, C					
1'				122.8, C		
2'	149.0, CH	8.67, s		129.6, CH	7.62, d (8.5)	
3'				115.8, CH	6.93, d (8.5)	
4'	150.2, CH	8.49, d (4.0)		156.7, CH		
5'	122.5, CH	7.16, dd (5.0, 5.0)		115.8, CH	6.93, d (8.5)	
6'	135.7, CH	7.79, d (8.0)		129.6, CH	7.62, d (8.5)	
1''	123.3, C			124.5, C		
2''	125.1, C			128.3, CH	6.46, d (2.0)	
3''	149.0, C			121.0, C		
4''	146.5, C			152.2, C		
5''	153.5, C			116.0, CH	6.52, d (8.0)	
6''	109.5, CH	7.29, s		131.5, CH	6.56, dd (8.0, 2.0)	
7''	165.0, C			122.1, CH	6.12, d (10.0)	
8''				130.6, CH	5.54, d (10.0)	
9''				76.8, C		
10''				26.8, CH ₃	1.27, s	
11''				27.9, CH ₃	1.37, s	

^aOverlapped signals. ^bChemical shifts of methoxy groups in 2: 3''-OMe δ_H 3.79 (s), δ_C 60.9; 4''-OMe δ_H 3.82 (s), δ_C 61.5; 5''-OMe δ_H 3.87 (s), δ_C 56.2; 7''-OMe δ_H 3.72 (s), δ_C 52.5. ^cChemical shift of methoxy groups in 3: 5-OMe δ_H 3.78 (s), δ_C 53.5. ^dNot observed.

those of 4 and differed only in the absence of one amide carbonyl signal (δ_C 163.2) in 4 and the appearance of a quaternary carbon signal (δ_C 131.5) in 2. Comparison of the molecular formulas of 2 and 4 also suggested that 2 might be produced by dehydration of 4. Heating 4 in pyridine at 100 °C for 8 h formed 2 in 80% yield, proving this hypothesis. This was

further confirmed by HMBC correlations between H-2' (δ_H 8.67)/H-6' (δ_H 7.79) and C-3 (δ_C 131.5). Furthermore, the carbon signal of C-1 shifted upfield from δ_C 168.1 (in 4) to δ_C 162.5 (in 2), revealing the existence of a quinazoline fragment as in terremide B.³ The structure of asperterrestide B (2) was determined as 3,4,5-trimethoxy-2-(4-oxo-2-(pyridine-3-yl)-quinazolin-3(4H)-yl) benzoate.

Aspernolide E (3) was assigned the molecular formula $C_{24}H_{22}O_7$ through an analysis of its HRESIMS data, requiring 14 degrees of unsaturation. From the 1H and ^{13}C NMR spectra (Table 2), signals for 1,2-disubstituted benzene protons at δ_H 7.62 (2H, d, J = 8.5 Hz) and 6.93 (2H, d, J = 8.5 Hz) and 1,2,4-trisubstituted benzene protons at δ_H 6.46 (1H, d, J = 2.0 Hz), 6.52 (d, J = 8.0 Hz), and 6.56 (dd, J = 8.0, 2.0 Hz) were recognized. Comparison of the 1H NMR data of 3 with those of aspernolide A (5) revealed one additional *cis*-double bond in 3.²³ In the HMBC spectrum, correlations from δ_H 6.12 (1H, d, J = 10.0 Hz) to C-4'' and C-9'' and from δ_H 5.54 (1H, d, J = 10.0 Hz) to C-3'' and C-9'' indicated the position of the double bond between C-7'' and C-8''. The similar specific rotation values of 3 ($[\alpha]_D^{30}$ +100) and aspernolide A ($[\alpha]_D^{28}$ +88.7) suggested the same *R* configuration at C-4.

Compound 1 showed cytotoxicity toward human carcinoma U937 and MOLT4 cell lines with IC_{50} values of 6.4 and 6.2 μM , respectively. In addition, compound 1 showed inhibitory effects on the influenza virus strains A/WSN/33 (H1N1) and A/Hong Kong/8/68 (H3N2) with IC_{50} values of 15 and 8.1 μM , respectively.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were determined with an MCP 300 (Anton Paar) polarimeter at 25 °C. UV spectra were recorded on a U-2910 spectrometer (Hitachi). NMR spectra were recorded with an Avance 500 spectrometer (Bruker) at 500 MHz for the 1H nucleus and 125 MHz for the ^{13}C nucleus. Chemical shifts (δ) are given with reference to TMS. ESIMS spectra were obtained with an Esquire 3000 Plus spectrometer (Bruker). HRESIMS data were acquired on a micro TOF-QII mass spectrometer (Bruker). Column chromatography was performed using silica gel (100–200 mesh; Qingdao Marine Chemicals) and Sephadex LH-20 (Amersham Pharmacia). HPLC was carried out on an ODS column (250 $\times$ 4.6 mm, 5 μm ; Phenomenex) with a photodiode array detector (Shimadzu).

Fungal Materials. The fungal strain of *Aspergillus terreus* SCSGAF0162 was isolated from the tissue of the gorgonian *Echinogorgia aurantiaca* collected from Sanya, Hainan Province, China. The strain was identified by one of the authors (X.-Y.Z.), and a voucher specimen (*A. terreus* SCSGAF0162) has been deposited in the RNAM Center for Marine Microbiology, South China Sea Institute of Oceanology, Chinese Academy of Sciences.

Fermentation and Isolation. The fungal strain *A. terreus* SCSGAF0162 was cultivated in 10 L of liquid medium (20 g D-sorbitol, 3.0 g yeast extract, 0.3 g $MgSO_4 \cdot 7H_2O$, 10 g L-lysine, 0.5 g KH_2PO_4 , 100 g maltose, 100 g NaCl in 1 L of water after adjusting its pH to 7.0, in 500 mL Erlenmeyer flasks each contain 200 mL of culture broth) at 28 °C without shaking for one month. The fermented whole broth (10 L) was filtered through cheesecloth to separate the supernatant from the mycelia, and the mycelia were extracted three times with acetone. The acetone solution was evaporated under reduced pressure to afford an aqueous solution, which was then extracted three times with EtOAc to afford the EtOAc extract (10 g). The EtOAc-soluble part (10 g) was chromatographed on silica gel using gradient elution from 100% (v/v) $CHCl_3$ to 100% MeOH (v/v), to give five fractions (Fr. A–E). Fr. A (100% $CHCl_3$) contained most of the nonpolar constituents such as fatty acids and sterols and was not further investigated. Fraction B ($CHCl_3$ /MeOH,

98:2–95:5 v/v elution, 1.2 g) was further purified by semipreparative reversed-phase HPLC (MeOH/H₂O, 70% v/v, 3 mL/min, UV detector 230 nm) to yield **3** (2 mg), butyrolactone I (10 mg), butyrolactone III (8 mg), butyrolactone II (5 mg), and 4-(4-hydroxyphenyl)-5-(4-hydroxyphenylmethyl)-2-hydroxyfuran-2-one (6 mg). Fraction C (CHCl₃/MeOH, 95:5–9:1 v/v elution, 2 g) was chromatographed on a C₁₈ silica gel column to afford five subfractions, C1–C5. Fr. C2 was subjected to semipreparative reversed-phase HPLC (MeOH/H₂O, 60% v/v, 3 mL/min, UV detector 250 nm), and compounds territre C (3 mg), territre B (5 mg), and territre A (3 mg) were isolated. Then Fr. C3 was purified by semipreparative reversed-phase HPLC (MeOH/H₂O, 50% v/v, 3 mL/min, UV detector 250 nm), resulting in the isolation of compounds arisugasin H (2 mg) and arisugasin D (6 mg). Fr. C4 followed by semipreparative reversed-phase HPLC (ACN/H₂O, 50% v/v, 3 mL/min, UV detector 230 nm) afforded compounds **1** (10 mg). Finally, Fr. C (CHCl₃/MeOH, 9:1–7:3 v/v elution, 800 mg) was further purified on a Sephadex LH-20 column (MeOH) and by semipreparative reversed-phase HPLC (CH₃CN/H₂O, 40% v/v, 3 mL/min, UV detector 230 nm) to yield **2** (2 mg) and **4** (5 mg).

Asperterrestide A (1): yellowish, amorphous powder; $[\alpha]_D^{30}$ –13 (c 0.03, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 220 (3.57) nm; ¹H and ¹³C NMR data, see Table 1; ESIMS m/z 503 [M + Na]⁺; HRESIMS m/z 503.2274 [M + Na]⁺ (calcd for C₂₆H₃₂N₄O₅Na, 503.2265).

Terremide C (2): yellowish, amorphous powder; $[\alpha]_D^{30}$ +40 (c 0.005, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 225 (4.41), 268 (3.22) nm; ¹H and ¹³C NMR data, see Table 2; ESIMS m/z 448 [M + H]⁺; HRESIMS m/z 448.1510 [M + H]⁺ (calcd for C₂₄H₂₂N₃O₆, 448.1503).

Aspernolide E (3): yellowish, amorphous powder; colorless gum; $[\alpha]_D^{30}$ +100 (c 0.002, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 228 (3.47), 325 (4.13) nm; ¹H and ¹³C NMR data see Table 2; ESIMS m/z 423 [M + H]⁺; HRESIMS m/z 423.1432 [M + H]⁺ (calcd for C₂₄H₂₃O₇, 423.1438).

Preparation of the (R)- and (S)-MTPA Ester Derivatives of 1. Compound **1** (0.6 mg) was transferred to a clean NMR tube and dried completely. Deuterated pyridine (0.5 mL), R-(–)-MTPA-Cl (12 μ L), and 0.2 mg of DMAP (4-dimethylaminopyridine) were added to the NMR tube under a N₂ gas stream. The reaction mixture was shaken for 5 h at room temperature to yield the (S)-MTPA ester derivative of **1** (**1a**). The ¹H NMR data of **1a** were directly obtained from the NMR tube, and the data were assigned on the basis of HMBC correlations. In the same fashion, the (R)-MTPA ester derivative of **1** (**1b**) was obtained from the reaction mixture of **1** (0.6 mg) in deuterated pyridine (0.5 mL), S-(+)-MTPA-Cl (12 μ L), and 0.2 mg of DMAP (0.2 mg). Key ¹H NMR shifts (ppm) for **1R** (500 M Hz, pyridine-*d*₅): 8.290 (H-6), 9.945 (NH-ABA), 6.473 (H-9), 6.933 (H-10), 7.529 (H-12/H-16), 3.047 (H-17), and for **1S** (500 M Hz, pyridine-*d*₅): 8.183 (H-6), 9.854 (NH-ABA), 6.486 (H-9), 7.043 (H-10), 7.723 (H-12/H-16), 3.030 (H-17).

Chiral-Phase HPLC Analysis of the Acid Hydrolysates of 1. To determine the absolute configurations of the Ala and Ile in **1**, chiral-phase HPLC analyses of the acid hydrolysates were conducted. Compound **1** (0.50 mg) was hydrolyzed as described. Two different analytical conditions were used to analyze the Ala and Ile isomers, respectively. First, the dried hydrolysate was dissolved in 100 μ L of 2 mM CuSO₄/H₂O solution. Ten microliters of this sample was analyzed by HPLC with a chiral-phase column (MCIGELCRS10W, 4.6 $\times$ 50 mm, Mitsubishi Chemical Corporation) using a 2 mM CuSO₄/H₂O solution as the mobile phase at a flow rate of 0.5 mL/min with UV detection at 254 nm. L-Ile, L-allo-Ile, D-Ile, and D-allo-Ile were detected as references. The retention times of D-Ile, D-allo-Ile, L-Ile, and L-allo-Ile were 13.6, 13.6, 31.2, and 22.4 min, respectively. Second, D-Ala and L-Ala were detected as references by HPLC with a chiral column (MCIGELCRS10W, 4.6 $\times$ 50 mm) using a 0.5 mM CuSO₄/H₂O solution as the mobile phase at a flow rate of 0.5 mL/min with UV detection at 254 nm. The retention times of D-Ala and L-Ala were 9.09 and 7.79 min, respectively. Hence, the Ala and Ile residues in **1** were determined to be D-Ala (8.71 min) and D-Ile or D-allo-Ile (13.1 min), respectively. Because the retention times of D-Ile and D-allo-Ile

were the same in this method, the configuration of the Ile residue was not further determined.

Cytotoxicity Assay. Due to the small amount of the new compounds, only compound **1** was tested for its cytotoxicity. Cytotoxic activity was evaluated using human leukemic monocyte lymphoma U937, erythroid leukemic K562, gastric carcinoma BGC-823, acute lymphoblastic leukemia MOLT-4, breast adenocarcinoma MCF-7, and lung carcinoma A549 cell lines by the MTT method as described previously.²⁴ Taxol was used as positive control against the U937, K562, BGC-823, MOLT-4, MCF7, and A549 cell lines with IC₅₀ values of 1.9, 4.9, 3.5, 1.8, 5.0, and 3.6 nM, respectively.

Antiviral Assay. Due to the small amount of the new compounds, only compound **1** was tested for its antiviral activity. Compound **1** was tested against influenza virus strain A/WSN/33 (H1N1) (an M2-resistant strain) and strain A/Hong Kong/8/68(H3N2) (an M2-sensitive strain) by CPE assay to determine its inhibitory effect against virus replication in the cell MDCK.²⁵ RIBA was used as positive control against H1N1 and H3N2 with IC₅₀ values of 20.2 and 0.41 μ M, respectively.

■ ASSOCIATED CONTENT

Supporting Information

This material (¹H, ¹³C NMR, DEPT, HSQC, HMBC, COSY, NOESY, ESI, and HRESIMS spectroscopic data for compounds **1**–**3**, ¹H NMR data for compounds **1a** and **1b**, HMBC spectroscopic data for **1a**, and Marfey's results) is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: shuhuaqi@scsio.ac.cn. Tel: (86) 20-89022112.

Notes

The authors declare no competing financial interest.

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