A New Cyclic Peptide and a New Steroid from the Fungus *Penicillium* sp. GD6 Isolated from the Mangrove *Bruguiera gymnorrhiza*

by **Zhen-Fang Zhou**[a]), **Xiao-Hong Yang**[b]), **Hai-Li Liu**[a]), **Yu-Cheng Gu**[c]), **Bo-Ping Ye***[b]), and **Yue-Wei Guo***[a])

[a]) State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, P. R. China (phone/fax: +86-21-50805813; e-mail: ywguo@simm.ac.cn)

[b]) School of Life Science & Technology, China Pharmaceutical University, Nanjing 210009, P. R. China (phone: +86-25-83271016; fax: +86-25-83271249; e-mail: yebp@cpu.edu.cn)

[c]) Syngenta Jealott's Hill International Research Centre, UK-Berkshire RG42 6EY

A rare new cyclic tetrapeptide, 5,5′-epoxy-MKN-349A (**1**), featured by a MKN-349A (**5**) skeleton and containing an uncommon ether bridge between C(5) and C(5′), and a new steroid, named 11-*O*-acetyl-NGA0187 (**2**), together with two known steroids, **3** and **4**, were isolated from an endophytic fungus *Penicillium* sp. GD6 associated with the Chinese mangrove *Bruguiera gymnorrhiza*. The structures of the new compounds were elucidated on the basis of extensive spectroscopic analyses and by comparison with the data of related compounds reported in literature. Neither of the compounds **3** and **4**, isolated in this study, showed obvious bioactivities in the antibacterial bioassay experiments.

Introduction. – Marine microorganisms, especially marine-derived fungi, are widely recognized as emerging sources of secondary metabolites [1]. Mangrove-associated fungi, the second largest ecological group of the marine-derived fungi, have been reported to produce a wide variety of structurally unique and biologically active compounds [2]. In particular, many fungi were recently isolated from the mangrove *Bruguiera gymnorrhiza*. Chemical investigation on these fungi led to the isolation of a number of bioactive compounds, such as meroterpenoids [3], dihydroisocoumarins [4], and biphenyl derivatives [5].

In the course of our continuing efforts aiming at searching for new bioactive substances from the marine microorganisms [6], a fungal strain *Penicillium* sp. GD6, recently isolated from the Chinese mangrove *B. gymnorrhiza* collected from Zhanjiang, China, was selected for further investigation, since the crude AcOEt extract showed potent antibacterial activity against *Staphylococcus aureus* with a *MIC* value of 6.4 μg/ml. A preliminary chemical investigation of the title fungus led to the isolation and identification of a novel pyrrolizidine alkaloid, named penibruguieramine A [7]. Our re-investigation on the crude extract of the culture of *Penicillium* sp. GD6 has now resulted in the isolation of a novel cyclic tetrapeptide, named 5,5′-epoxy-MKN-349A (**1**), and a new steroid, 11-*O*-acetyl-NGA0187 (**2**), along with two known steroids **3** and **4**. The new peptide **1** shares the same structural framework as the previously reported cyclopeptide MKN-349A (**5**), but possesses an additional ether bridge between C(5) and C(5′). Herein, we report the isolation and structure elucidation of the two new compounds **1** and **2** (*Fig. 1*).

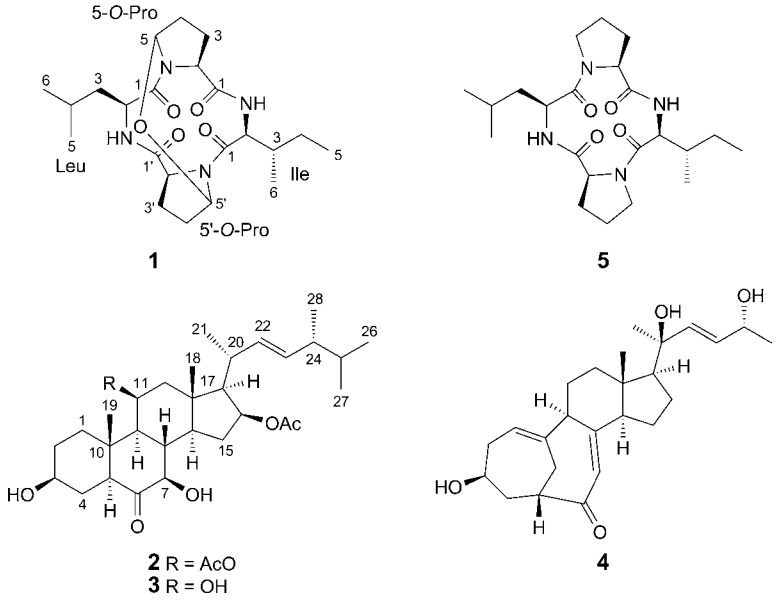

Fig. 1. *Structures of compounds* **1**–**5**

Results and Discussion. – The whole culture of *Penicillium* sp. GD6 was extracted with AcOEt and BuOH after a static fermentation (300 ml × 100 flasks) for 30 days. The AcOEt-soluble fractions were repeatedly chromatographed on silica gel, reversed-phase (RP)-C_{18} silica gel, and RP-HPLC column to afford pure compounds **1** (0.8 mg) and **2** (0.6 mg), together with two known steroids.

The structures of the known steroids were readily identified as NGA0187 (**3**) [8] and cyclocitrinol (**4**) [9] by comparison of their spectroscopic data with those reported in the literature.

Compound **1** was isolated as optically active, white amorphous powder. The molecular formula, $C_{22}H_{34}N_4O_5$, was determined by the HR-ESI-MS (*m*/*z* 457.2418 ($[M+Na]^+$, calc. 457.2427)), suggesting eight degrees of unsaturation. The IR spectrum of **1** exhibited absorption bands at 3424 and 1676 cm^{-1}, implying the presence of the amide functional groups. Further, the presence of the four amide functionalities were deduced by the observation of the resonances arising from four C=O C-atoms (δ(C) 166.6, 167.6, 169.6, and 171.2) and four N-containing CH groups (δ(C) 60.4, 57.6, 57.2, and 53.3) in the ^{13}C-NMR and DEPT spectra (*Table*), indicating the tetrapeptide nature of the isolate. Moreover, due to its negative reaction to ninhydrin [10], **1** was inferred to be a cyclotetrapeptide.

A literature search revealed that the ^{13}C-NMR data of **1** showed similarities with those of the model cyclopeptide, MKN-349A (**5**; *Table*), which was previously isolated from a marine-derived bacterium of the genus *Nocardiopsis* [11]. Actually, careful comparison of the ^{13}C-NMR data of **1** with those of **5** revealed clearly that both **1** and **5** contain the same Ile and Leu residues that were further confirmed by careful analyses of the 2D-NMR spectra, including HSQC, COSY, and HMBC (*Fig. 2*). In fact, the

Table. *^{1}H- and ^{13}C-NMR Data for Compounds* **1** *and* **5**

Moiety	Position	**1**		**5** [11]
		δ(H)[a])	δ(C)[b])	δ(C)
5-*O*-Pro/Pro (I)	1		171.2 (*s*)[c])	172.4 (*s*)
	2	4.31–4.38 (*m*)	57.2 (*d*)	60.0 (*d*)
	3	2.33–2.38 (*m*), 1.81–1.87 (*m*)	30.9 (*t*)	29.5 (*t*)
	4	2.38–2.44 (*m*)	26.8 (*t*)	23.2 (*t*)
	5	5.70–5.77 (*m*)	82.1 (*d*)	46.2 (*t*)
Ile	1		166.6 (*s*)	167.6 (*s*)
	2	3.97–4.01 (*m*)	60.4 (*d*)	61.3 (*d*)
	3	2.27–2.31 (*m*)	35.2 (*d*)	37.1 (*d*)
	4	1.39–1.42 (*m*), 1.18–1.25 (*m*)	24.0 (*t*)	25.4 (*t*)
	5	0.93 (*t*, *J* = 6.8)	12.0 (*q*)	12.6 (*q*)
	6	1.05 (*d*, *J* = 7.2)	15.9 (*q*)	15.5 (*q*)
5′-*O*-Pro/Pro (II)	1′/1		169.6 (*s*)	171.6 (*s*)
	2′/2	4.31–4.38 (*m*)	57.6 (*d*)	59.3 (*d*)
	3′/3	2.33–2.38 (*m*), 1.81–1.87 (*m*)	30.9 (*t*)	29.9 (*t*)
	4′/4	2.27–2.31 (*m*)	26.2 (*t*)	23.1 (*t*)
	5′/5	5.70–5.77 (*m*)	82.0 (*d*)	46.7 (*t*)
Leu	1		167.6 (*s*)	169.1 (*s*)
	2	4.06 (*dd*, *J* = 10.9, 3.3)	53.3 (*d*)	57.1 (*d*)
	3	1.99–2.06 (*m*), 1.54 (*ddd*, *J* = 14.6, 10.1, 5.1)	38.4 (*t*)	43.7 (*t*)
	4	1.74–1.75 (*m*)	24.6 (*d*)	25.5 (*d*)
	5	1.01 (*d*, *J* = 6.6)	23.3 (*q*)	23.3 (*q*)
	6	0.96 (*d*, *J* = 6.6)	21.1 (*q*)	21.9 (*q*)

[a]) Recorded at 500 MHz in $CDCl_3$. [b]) Recorded at 125 MHz in $CDCl_3$. [c]) Assigned by HMBC spectrum.

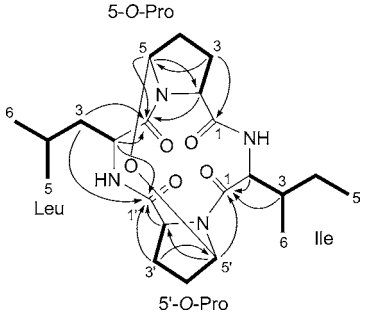

Fig. 2. *^{1}H,^{1}H-COSY* (—) *Correlations and selected key HMBCs* (H → C) *of* **1**

main differences between **1** and **5** were the disappearance of two CH_2 groups at C(5) in the two Pro residues in **5** (δ(C) 46.2 and 46.7), accompanying the appearance of two O-bearing CH groups resonating at δ(C) 82.0 and 82.1 in **1** (*Table*).

The identification of the other two amino acid moieties was accomplished by extensive interpretation of the 2D-NMR spectra of **1**. Considering the cyclotetrapeptide nature of **1**, the remaining unassigned signals in the NMR spectra should

be ascribed to the additional two amino acid moieties. Detailed analysis of the ^{1}H-NMR spectra revealed that two sets of ^{1}H-NMR signals for the other two amino acid moieties were heavily overlapped. Particularly, the well-resolved ^{1}H-NMR resonances at δ(H) 5.70–5.77 (H–C(5) and H–C(5′)) and 4.31–4.38 (H–C(2) and H–C(2′)) (*Table*) were each integrated for two H-atoms, ascribable to four N-bearing CH groups. In the ^{13}C-NMR spectrum, only slight differences for two series of similar ^{13}C-NMR resonances were observed (*Table*). The above observations indicate that the structures of the two amino acid residues are probably the same. Analyses of the COSY and HSQC spectra of **1** allowed the identification of the spin system X–CH–CH_2–CH_2–CH–X′ (*Fig. 2*). The N-bearing CH (δ(H) 4.31–4.38 (H–C(2)); δ(C) 57.2) exhibited clear correlations with the adjacent CH_2 H-atoms (δ(H) 2.33–2.38 and 1.81–1.87 (CH_2(3))), which, in turn, were further correlated with the CH_2 H-atoms resonating at δ(H) 2.38–2.44 (CH_2(4)). The connection CH_2(4)/H–C(5) was established by the cross-peak from the CH_2 H-atoms (δ(H) 2.38–2.44 (CH_2(4))) to the O-bearing CH group (δ(H) 5.70–5.77 (H–C(5)); δ(C) 82.1). Finally, the key HMBC from H–C(5) (δ(H) 5.70–5.77) to the N-bearing CH C-atom (δ(C) 57.2 (C(2))) defined the structure of a pyrrolidine ring, indicating the presence of an *O*-substituted proline residue. Thus, the structure for the third residue, namely 5-*O*-Pro, was established. Analogously, the structure of 5′-*O*-Pro moiety was determined by detailed interpretation of the ^{1}H,^{1}H-COSY, HSQC, and HMBC spectra.

With the identification of four amino acid residues, the connectivity of these residues to complete the structure was established by HMBC experiments (*Fig. 2*). By analogy with the model compound **5** [11], the diagnostic HMBCs from H–C(2) (δ(H) 4.31–4.38) and H–C(5) (δ(H) 5.70–5.77) in 5-*O*-Pro to the C=O C-atom (δ(C) 167.6) of Leu allowed the connection of 5-*O*-Pro and Leu. Correlations of the H-atom signals at δ(H) 4.06 (H–C(2) of Leu), and 1.54 and 1.99–2.06 (CH_2(3) of Leu) to the C=O C-atom (δ(C) 169.6) of 5′-*O*-Pro evidenced a peptide linkage between Leu and 5′-*O*-Pro. The presence of a peptide linkage between 5′-*O*-Pro and Ile was secured by correlations of the C=O C-atom (δ(C) 166.6) with H-atoms (δ(H) 5.70–5.77 (H–C(5′)) of 5′-*O*-Pro. Although the long-range correlations between C(1) (δ(C) 171.2) of 5-*O*-Pro and H–C(2) (δ(H) 3.97–4.01) of Ile were not observed in the HMBC spectrum, considering the cyclic peptide nature of **1** and the almost identical chemical shift values of C(1) in 5-*O*-Pro and C(2) in Ile to those of **5** (*Table*), it is obvious that there is a peptide linkage between C(1) in 5-*O*-Pro and N-atom of Ile. The backbone of **1** was thus determined as the same as that of MKN-349A (**5**) (*Fig. 1*) [11].

Subtraction of the atoms present in the above elaborated macrocyclic core from the molecular formula of **1** indicated that the only unassigned O-atom has to form the ether bridge between C(5) and C(5′) according to the unsaturation degree required by the molecular formula, and the downfield ^{13}C-NMR chemical shifts for C(5) and C(5′). As a consequence, the constitution of 5,5′-epoxy-MKN-349A (**1**) was thus elucidated as shown in *Fig. 1*.

With the gross structure of **1** being solved, the next task was to determine the absolute configuration of the amino acid residues and the configuration of the ether bridge. Unfortunately, the limited amount and the unstable nature of compound **1** prevented us from assigning the absolute configuration of each amino acid residue by *Marfey*'s methodology [12], and determining the relative configuration of the ether

bridge. However, on the basis of biogenetic consideration, L-configurations are tentatively suggested for all four amino acid residues. This assignment was further supported by the negative optical rotation sign of **1** [13]. It may be worth to point out that the C-atom signals of **1** were observed in pairs in the ratio of *ca.* 3:1 in the ^{13}C-NMR spectrum. This phenomenon could be rationalized due to the adoption of different conformations of the amide bonds of the 5-*O*-Pro-Leu and the 5′-*O*-Pro-IIe, usually observed in the proline-rich peptides [14].

Now, we can conclude that compound **1** has a same cyclotetrapeptide skeleton as the model compound **5** [11], but possesses an uncommon ether bridge between C(5) and C(5′). To the best of our knowledge, compound **1** is the first example of a cyclotetrapeptide with an ether bridge.

Besides the above mentioned cyclotetrapeptide, three steroids, **2**–**4**, of which **2** was new, were also isolated. The structure elucidation of **2** was straightforward by comparing the NMR data of **2** with those of the co-occurring steroid, NGA0187 (**3**), isolated previously from the fermentation broth of *Acremonium* sp. [15]. A comparison of overall ^{1}H- and ^{13}C-NMR data of compounds **2** and **3** revealed great similarities between them. In fact, **2** differs from **3** only by the presence of an additional *O*-Ac functionality, which was evidenced by the resonances at δ(H) 2.04 in its ^{1}H-NMR spectrum, and at δ(C) 169.8 and 21.7 in its ^{13}C-NMR spectrum (*Exper. Part*). Since the corresponding H-atom signal of H–C(11) was shifted downfield from δ(H) 4.39 in **3** [8] to δ(H) 5.41 in **2**, the acetylation was determined to occur at *O*–C(11), which was further supported by the obvious COSY correlations between H–C(11) (δ(H) 5.41) and CH_2(12) (δ(H) 2.27–2.31 and 1.35–1.42). Therefore, compound **2** was established as the 11-*O*-Ac derivative of **3**, consistent with 42 mass unit difference between **2** and **3**.

Compounds **3** and **4** were tested for their antibacterial activities against the methicillin-sensitive *S. aureus Newman* strain. Unfortunately, they were inactive at the concentration of 320 μg/ml. Due to the scarcity of compounds **1** and **2**, and the unstability of compound **1**, their antibacterial activities could not be evaluated.

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Experimental Part

General. Anal. TLC: Precoated silica gel plates (SiO_2; *Yantai Zifu Chemical Group Co.*, *G60 F_{254}*). Column chromatography (CC): commercial SiO_2 (*Qingdao Haiyang Chemical Group Co.*, 200–300 mesh). Reversed-phase (RP) HPLC: *Shimadzu LC-6AD* series liquid chromatography with a *Diode Array Detector* at 210 nm and a semi-prep. *Eclipse XDB-C18* column (250 mm × 9.4 mm i.d., 5-μm particle size). Optical rotations: *PerkinElmer 341* polarimeter. IR Spectra: *Nicolet-Magna FT-IR 750* spectrometer; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker DRX 500* equipped with a *TCI CryoProbe*; δ in ppm rel. to solvent ($CDCl_3$) residue $CHCl_3$ (δ(H) 7.26 ppm; δ(C) 77.0 ppm) as internal standard; *J* in Hz; the assignments were supported by ^{1}H,^{1}H-COSY, HSQC, and HMBC experiments. HR-ESI-MS: *Q-TOF Micro* LC/MS-MS mass spectrometer; in *m*/*z*.

Fungal Material. The fungal strain GD6 was isolated from the stem bark of *B. gymnorrhiza* collected in Zhanjiang, China, in April 10, 2009. It was initially identified as *Penicillium* species based on its morphological characters and the internal transcribed spacer (ITS) sequence (accession No. in GenBank: KF 604117). The frozen samples of this fungus are deposited with the School of Life Science & Technology in China Pharmaceutical University (Sample GD6).

Fermentation, Extraction, and Isolation. The whole cultures (100 × 300 ml flasks) were filtered through a four-layer cheesecloth to separate mycelia from broth. The broth was extracted with AcOEt to give an evaporated extract (11.27 g). The dried mycelia were homogenized and extracted with $CHCl_3$/MeOH 1:1, and the evaporated extract was partitioned between AcOEt and H_2O to yield an AcOEt-soluble extract (9.89 g). These two parts were combined for further separation based on their identical TLC profiles. This extract was separated by CC (*MCI* gel; MeOH/H_2O 50:50 to 100:0) to give seven fractions, *Frs. A – G. Fr. A* was subjected to CC (SiO_2; petroleum ether (PE)/acetone 8:2 to 1:1) eluent to obtain three subfraction, *Frs. A1 – A3*. *Fr. A3* was purified by reversed-phase-HPLC (MeOH/H_2O 60:40) to yield **1** (0.8 mg). *Fr. E* was separated by CC (SiO_2; PE/AcOEt 7:3 to 1:9), and purified by RR *C18* SiO_2 (MeOH/H_2O 50:50 to 70:30) to give **4** (1.6 mg). *Fr. F* was subjected to CC (SiO_2; CH_2Cl_2/MeOH 100:1 to 20:1) to afford **2** (0.6 mg) and **3** (1.6 mg), resp.

5,5′-Epoxy-MKN-349A (= *(3*S*,6*S*,8a*S*,11*S*,14*S*,16a*S*)-Dodecahydro-6-[(1*S*)-1-methylpropyl]-14-(2-methylpropyl)-3,11-epoxydipyrrolo[1,2-*a*:1′,2′-*g*][1,4,7,10]tetraazacyclododecine-5,8,13,16-tetrone*; **1**). White amorphous powder. $[\alpha]_D^{20} = -62.8$ ($c = 0.07$, MeOH). IR: 3424 (br.), 2961, 2924, 2853, 1676, 1262, 1096, 802. ^{1}H- and ^{13}C-NMR: see the *Table*. HR-ESI-MS: 457.2418 ($[M+Na]^+$, $C_{22}H_{34}N_4NaO_5^+$; calc. 457.2427).

11-O-*Acetyl-NGA0187* (= *(3β,5α,7β,11β,16β,22*E*)-3,7-Dihydroxy-6-oxoergost-22-ene-11,16-diyl Diacetate* = *(3*S*,5*S*,7*R*,8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,16*S*,17*R*)-17-[(2*R*,3*E*,5*R*)-5,6-Dimethylhept-3-en-2-yl]hexadecahydro-3,7-dihydroxy-10,13-dimethyl-6-oxo-1*H*-cyclopenta[*a*]phenanthrene-11,16-diyl Diacetate*; **2**). White amorphous powder. $[\alpha]_D^{20} = +47.0$ ($c = 0.05$, $CHCl_3$). IR: 3427, 2962, 2925, 2854, 1739, 1463, 1378, 1261, 1095, 1021, 801. ^{1}H-NMR ($CDCl_3$, 500 MHz): 5.41 (*dd*, $J = 5.0$, 2.4, H–C(11)); 5.14 – 5.17 (*m*, H–C(22), H–C(23)); 5.11 (*dd*, $J = 12.4$, 7.7, H–C(16)); 3.74 (*d*, $J = 8.6$, H–C(7)); 3.67 (*d*, $J = 8.7$, H–C(3)); 2.62 – 2.67 (*m*, H_a–C(15)); 2.49 – 2.52 (*m*, H–C(20)); 2.27 – 2.31 (*m*, H–C(5), H_a–C(12)); 2.15 – 2.19 (*m*, H–C(8)); 2.04 (*s*, 11-AcO); 1.98 (*s*, 16-AcO); 1.85 – 1.90 (*m*, H_a–C(2), H_a–C(4)); 1.77 – 1.79 (*m*, H–C(24)); 1.65 – 1.70 (*m*, H_a–C(1)); 1.47 – 1.49 (*m*, H_a–C(9)); 1.35 – 1.42 (*m*, H_b–C(1), H_b–C(12), H–C(14), H_b–C(15), H–C(25)); 1.22 – 1.25 (*m*, H_b–C(2), H_b–C(4), H–C(17)); 1.03 (*s*, Me(18)); 1.01 (*d*, $J = 6.7$, Me(21)); 0.86 (*d*, $J = 6.8$, Me(28)); 0.81 (*s*, Me(19)); 0.81 (*d*, $J = 6.8$, Me(27)); 0.79 (*d*, $J = 6.8$, Me(26)). ^{13}C-NMR ($CDCl_3$, 125 MHz): Not detected for C(6); 170.0 (*s*, 16-AcO); 169.8 (*s*, 11-AcO); 134.7 (*d*, C(22)); 133.1 (*d*, C(23)); 78.5 (*d*, C(7)); 74.5 (*d*, C(16)); 69.9 (*d*, C(3)); 69.8 (*d*, C(11)); 60.1 (*d*, C(17)); 55.8 (*d*, C(14)); 54.4 (*d*, C(5)); 54.2 (*d*, C(9)); 44.2 (*t*, C(12)); 43.6 (*s*, C(10)); 43.3 (*s*, C(13)); 43.3 (*d*, C(24)); 42.8 (*d*, C(8)); 36.3 (2*t*, C(1), C(15)); 34.2 (*d*, C(20)); 33.0 (*d*, C(25)); 30.1 (*t*, C(2)); 29.1 (*t*, C(4)); 21.7 (*q*, 11-AcO); 21.5 (*q*, 16-AcO); 21.1 (*q*, C(21)); 20.1 (*q*, C(27)); 19.7 (*q*, C(26)); 18.0 (*q*, C(28)); 15.5 (*q*, C(19)); 14.9 (*q*, C(18)). HR-ESI-MS: 569.3474 ($[M+Na]^+$, $C_{32}H_{50}NaO_7^+$; calc. 569.3454).

Antibacterial Assay. The antimicrobial activities of the crude AcOEt extract of GD6, and compounds **3** and **4** against *S. aureus Newman* strain were evaluated by *MIC* (minimum inhibitory concentration) method. All the compounds were diluted with culture broth to 320 μg/ml as the initial concentration. Further 1:2 serial dilutions were performed by addition of culture broth to reach concentrations ranging from 160 to 0.3125 μg/ml. 100 μl of each dilution was distributed in 96-well plates, as well as sterility controls and growth controls (containing culture broth plus DMSO, without compounds). Each test and growth control well was inoculated with 5 μl of a bacterial suspension (*ca.* 10^5 CFU/well). The 96-well plates were incubated at 37° for 16 h. *MIC* Values of the compounds against *S. aureus Newman* strain were defined as the lowest concentration to inhibit the bacterial growth completely.

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