

Phenols and diketopiperazines isolated from Antarctic-derived fungi, *Penicillium citreonigrum* SP-6

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ABSTRACT

One diketopiperazine (**1**) and three phenols (**3**, **5** and **6**) were isolated from static culture of Antarctic fungus, *Penicillium citreonigrum* SP-6, as well as their structures were determined by NMR and CD spectroscopic methods. Additionally, two known compounds, *cyclo*-(*L*-Trp-*L*-Phe) (**2**) and (-)-(3*S*, 10*R*)-dichlorodiaportal (**4**), were isolated and identified. Antitumor biological studies demonstrated that compounds **1** and **3** showed weak inhibitions against HCT116 cancer cell lines with IC₅₀ values of 26.7 and 46.3 μM, respectively, comparing to cis-dichlorodiamine platinum.

1. Introduction

The genus *Penicillium* is a well-known producer of natural compounds including indole alkaloids (Li, 2010), sesquiterpenoid (Vansteelandt et al., 2013), polyketides (Ren et al., 2006; Kossuga et al., 2013) and hydroisocoumarins (Qi et al., 2013). These compounds have displayed various biological activities such as cytotoxic (Li, 2010; Vansteelandt et al., 2013), antibacterial (Qi et al., 2013), and antifouling (Ren et al., 2006). Nowadays, many research groups focus on Antarctic fungus due to its new and interesting source of microbes as well as many bioactive compounds isolated from these fungus (Wang et al., 2017; Figueroa et al., 2015; Zhou et al., 2015; Wu et al., 2013; Wang et al., 2016; Lin et al., 2014; Wu et al., 2012; Wang et al., 2015). Therefore, we focused on the exploration of secondary metabolites produced by Antarctic-derived fungi (Li et al., 2018). In this study, *Penicillium citreonigrum* SP-6, which was isolated from soil around the China Great Wall Station, was selected for further research due to its cytotoxic activities. Totally, one diketopiperazine (**1**) and three phenols (**3**, **5** and **6**) together with two known compounds, *cyclo*-(*L*-Trp-*L*-Phe) (**2**) and (-)-(3*S*, 10*R*)-dichlorodiaportal (**4**), were isolated from *Penicillium citreonigrum* SP-6 (see Fig. 1). This study elucidated the isolation procedure, structural identification and anticancer activities of the compounds from this fungus.

2. Results and discussion

Compound **1**, white amorphous power, showed its positive HRESIMS ions at *m/z* 366.1451 (calcd for C₂₀H₂₀N₃O₄⁺, 366.1448). The ¹H NMR spectrum of **1** (Table 1) afforded one mono-substituted aromatic ring (δ_H 7.01 (2H, d, *J* = 7.5 Hz, H-19, 23), 7.05 (2H, d, *J* = 7.5 Hz, H-20, 22), 6.86 (1H, t, *J* = 7.5 Hz, H-21)) and one ortho-disubstituted ring (δ_H 7.05 (1H, d, *J* = 7.2 Hz, H-4), 6.75 (1H, t, *J* = 7.2 Hz, H-5), 7.15 (1H, t, *J* = 7.2 Hz, H-6) and 6.71 (1H, d, *J* = 7.2, H-7)). Combined HSQC spectrum, the other hydrogen nuclear signals were assigned as two methylene signals (δ_H 2.15 (1H, H-10α), 1.43 (1H, H-10β), δ_C 36.8 (C-10); δ_H 2.98 (1H, H-17α), 2.81 (1H, H-17β), δ_C 40.1 (C-17), respectively), two N-substituted methine units (δ_H 4.38 (1H, H-11), δ_C 56.4 (C-11); δ_H 4.30 (1H, H-14), δ_C 56.9 (C-14), respectively) and one methine signal (δ_H 5.28 (1H, s, H-2), δ_C 101.8 (C-2)). Through the comparison of the NMR data of **1** with *Cyclo*-(*L*-Trp-*L*-Phe) (Kahina et al., 2015) indicated that the highly similarity of their structures, except for forming a 1, 2-dioxetane unit between C-2 (δ_C 101.8) and C-3 (δ_C 76.6) in **1**.

The stereochemistry of compound **1** was determined by biosynthesis pathway and theoretical ECD (electronic circular dichroism) methods. The 11*S* and 14*S* of **1** could be deduced by its biosynthesis pathway because it might be peroxidated from compound **2**, *Cyclo*-(*L*-Trp-*L*-Phe). The stereochemistry of **1** had been performed as 2*R*, 3*R*, 11*S* and 14*S* which were further evidenced by comparing CD experimental with

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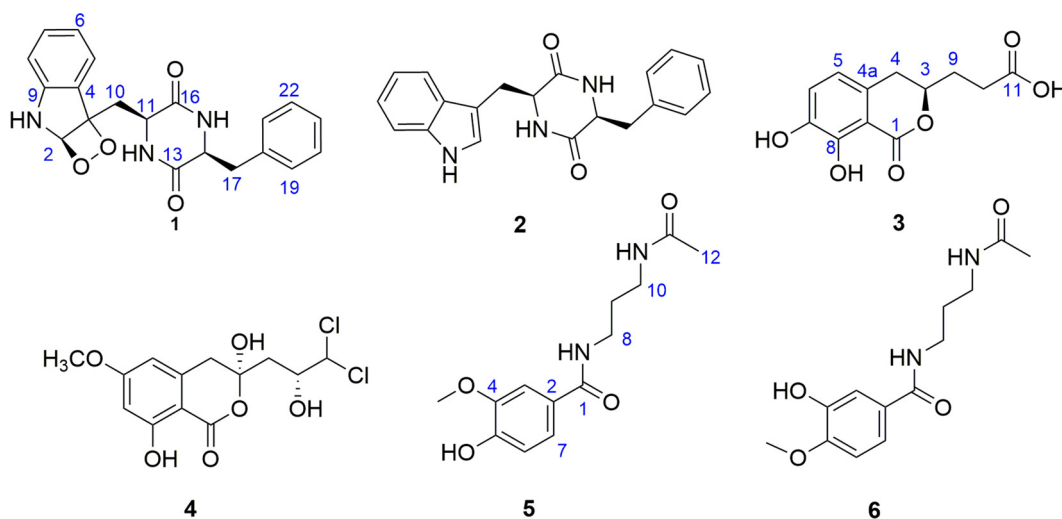


Fig. 1. Structures of the isolated compounds 1-6 from *Penicillium citreonigrum*.

Table 1

NMR spectrum data of compound 1 in CD₃OD.

No.	¹³ C ^a	¹ H ^b (J Hz)	HMBC ^c
2	101.8	5.28(1H,s)	C3,C9,C10
3	76.6		
4	124.6	7.05 (1H, d, 7.2)	C3,C6,C9
5	120.6	6.75 (1H, t, 7.2)	C6,C8
6	131.7	7.15 (1H, t, 7.2)	C4,C9
7	111.3	6.71 (1H, d, 7.2)	C4,C5,C8
8	132.2		
9	149.5		
10	36.8	α 2.15 (1H, dd, 13.8, 5.5) β 1.43 (1H, dd, 13.8, 8.3)	C2,C3,C5,C11,C16
11	56.4	4.38 (1H, dd, 8.3, 5.5)	C3,C10,C13,C16
13	168.5		
14	56.9	4.30 (1H, t, 4.9)	C13,C16,C17,C18
16	164.0		
17	40.1	α 2.98(1H, dd, 13.9, 4.9) β 2.81 (1H, dd, 13.9, 4.9)	C13,C14,C18,C19,C23
18	136.7		
19, 23	131.7	7.01(2H, d, 7.5)	C17,C21
20, 22	130.0	7.05(2H, d, 7.5)	C18,C21
21	128.4	6.86 (1H, t, 7.5)	C19,C23

^a 125 MHz for ¹³C NMR.

^b 500 MHz for ¹H NMR.

^c 500 MHz for 2D NMR.

theoretical ECD data (Fig. S1). Above all, the structure of compound 1 enlightened 2R, 3R- dioxeto-Cyclo-(L-Trp-L-Phe).

Compound 3, known as white amorphous powder, was identified to have the molecular formula C₁₂H₁₂O₆ on the basis of positive HRESIMS data, *m/z* 275.0531 [M + Na]⁺ (calcd for C₁₂H₁₃O₆Na⁺, 275.0526). The ¹H NMR spectrum (Table 2) of 3 showed the presence of three methylene units (δ_H 2.95 (1H, dd, *J*₁ = 3.0 Hz, *J*₂ = 16.0 Hz, H-4α), 2.87 (1H, dd, *J*₁ = 11.0 Hz, *J*₂ = 16.0 Hz, H-4β), 2.55 (2H, m, H-9) and 2.07 (2H, m, H-10)), one oxygenated methine (δ_H 4.63(1H, m, H-3)), two aromatic hydrogen signals with AB coupling system (δ_H 6.64 (1H, d, *J* = 8.0, H-5) and 7.00 (1H, d, *J* = 8.0, H-6)). The ¹³C NMR and HSQC spectrum demonstrated 12 carbon signals, including six non-protonated carbons, three methines and three methylene units. An aromatic ring was deduced in the molecule by the AB coupling system of ¹H NMR and the ¹³C NMR data δ_C 131.1 (C-4a), 119.0 (C-5), 122.9 (C-6), 145.9 (C-7), 151.6 (C-8) and 109.7(C-8a). Furthermore, H-4 correlated to C-3, C-4a, C-5, C-7, C-8a and C-9 in HMBC spectrum (Table 2 and Fig. 2) basically indicated that the skeleton of compound 3 is dihydro-isocoumarin (Rukachaisirikul et al., 2009; Hussain et al., 2009). The completed assignments of ¹H and ¹³C NMR data were well

Table 2

NMR Spectrum data of compound 3 in CD₃OD.

	¹³ C ^a	¹ H ^b (J Hz)	Key HMBC ^c
1	171.7		
3	81.3	4.63 (1H, m)	C4
4	33.2	α 2.95 (1H, dd, 3.0, 16.0) β 2.87(1H, dd, 11.0, 16.0)	C3, C4a, C5, C7, C8a, C9
4a	131.1		
5	119.0	6.64 (1H, d, 8.0)	C1, C4, C6, C7, C8, C8a
6	122.9	7.00 (1H, d, 8.0)	C4a, C7, C8
7	145.9		
8	151.6		
8a	109.7		
9	30.4	2.55 (2H, m)	C3, C10, C11
10	31.1	2.07 (2H, m)	C3, C4, C9, C11
11	176.6		

^a 125 MHz for ¹³C NMR.

^b 500 MHz for ¹H NMR.

^c 500 MHz for 2D NMR.

elucidated by HMBC spectrum. For example, the C-7 was especially assigned as δ_C 145.9 by strong correlation with H-6 and relatively weak correlation with H-5, respectively, due to ²*J*_{H-C} and ⁴*J*_{H-C} coupling between the hetero-nuclear. In addition, the 7,8-dihydroxy of aromatic ring were further evidenced by comparing ¹³C NMR data of C-7 (δ_C 145.9) and C-8 (δ_C 151.6) with the reported NMR data of 7,8-dihydroxy and 5,8-dihydroxy isocoumarin (Hussain et al., 2009), in which the chemical shifts of C-7 and C-8 appeared at δ_C 145.2 and δ_C 155.0 in 7,8-dihydroxy isocoumarin, while δ_C 143.5(C-7) and 146.2 (C-8) were shown in 5,8-dihydroxy isocoumarin (Qi et al., 2013), respectively. The absolute configuration 3R of 3 was determined by comparison of experimental with theoretical ECD (electronic circular dichroism, shown in Fig. S2). Thus, the structure of compound 3 was elucidated as 3R-(7, 8-dihydroxy- 1-oxoisochroman-3-yl) propanoic acid.

Compound 5, white amorphous powder, afforded the molecular formula C₁₃H₁₈N₂O₄ by the positive HRESIMS data, *m/z* 267.1340 [M + H]⁺ (calcd for C₁₃H₁₉N₂O₄, 267.1339). The ¹H NMR spectrum of compound 5 (Table 3) demonstrated three aromatic signals (δ_H 7.48 (1H, s), 7.39 (1H, d, *J* = 8.0 Hz) and 6.87 (1H, d, *J* = 8.0 Hz)), one oxygenated methyl (δ_H 3.94 (3H, s)), three methylene units (δ_H 3.43 (2H, t, *J* = 6.5 Hz), 3.29 (2H, t, *J* = 6.5 Hz), 1.81 (2H, t, *J* = 6.5 Hz)) and one methyl signal (δ_H 1.99 (3H, s)). The ¹³C NMR and HSQC spectrum (Table 3) showed total 13 carbon signals, including two carbonylic carbon signals (δ_C 173.6 and 170.1), six aromatic carbon signals (δ_C 151.5, 149.0, 127.0, 122.1, 116.1 and 112.2), one oxygenated

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