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Isolation of Talathermophilins from the Thermophilic Fungus *Talaromyces thermophilus* YM3-4

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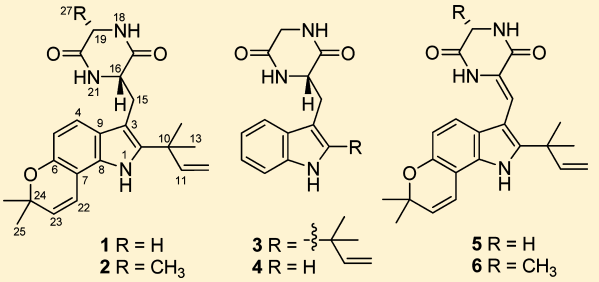
Supporting Information

ABSTRACT: Six indole alkaloids with various levels of prenylation were isolated from the thermophilic fungus *Talaromyces thermophilus* strain YM3-4. Their structures were identified by NMR and MS spectroscopic analyses. Compounds **1** and **2** are new analogues of the key versatile precursor notoamide E. Compound **3** is a novel analogue of preechinulin, and compound **4** was reported as a natural occurring cyclo(glycyltryptophyl) for the first time. The metabolite profile of this thermophilic organism displayed a biosynthetic pathway for talathermophilins.



The prenylated indole alkaloids produced by various genera of fungi, in particular *Aspergillus* and *Penicillium* spp., have generated considerable interest and have become the target of synthetic studies because of their structural diversity (Figure 1) and their promising biological activities.[1] Almost 100 members of this family of secondary metabolites have been reported, including aspergamides, avrainvillamide, stephacidins, sclerotiamide, deoxybrevianamides, echinulins, neoechinulins, fellutanines, marcfortines, paraherquamides, piscarinine, tryprostatin, norgeamides, and notoamides.[1,2] From a biosynthetic perspective, a scaffold of 3-((1,7-dihydro-7,7-dimethyl-2-(2-methylbut-3-en-2-yl)pyrano[2,3-*g*]indol-3-yl)methyl)-piperazine-2,5-dione as possessed by intermediates **I**–**III** has been regarded as a critical biosynthetic point, since it symbolizes the transition of simple prenylated indole alkaloids to more complex pyranoindole alkaloids (Figure 1). Among them, intermediate **III**, which was named notoamide E, has long been proposed as a key versatile precursor in the biosynthetic pathways for the prenylated indole alkaloids derived from proline.[3]

Thermophilic fungi are extremophiles with an optimum growth temperature of 50 °C or more, a minimum of about 40 °C, and a maximum of up to more than 70 °C.[4] They are commonly found in geothermally heated regions of the Earth such as hot springs and deep sea hydrothermal vents, as well as decaying plant matter such as peat bogs and compost. Thermophilic fungi have been a considered potential source of thermostable enzymes with scientific and commercial interest; for example, fungi from compost have attracted attention due to their ability to degrade polysaccharide constituents of biomass and help to decompose various plant materials.[5] However, investigations on secondary metabolites of thermophilic fungi have not received much publicity and attention.

Recently, we reported results from a chemical investigation on the pigments of the thermophilic fungal strain *Talaromyces thermophilus* YM1-3 led to the isolation of two new prenylated tryptophan alkaloids, talathermophilins A and B (**5** and **6**).[6] These two compounds were the first examples of pyranoindol alkaloids derived from glycine and alanine, respectively, and interestingly were dehydro derivatives of the two biosynthetic intermediates **I** and **II**. Both compounds showed nematicidal toxicity (ca. 38% and 44% inhibition, respectively) toward the free-living nematode *Panagrellus redivevus* at a concentration of 400 μg/mL but were not active in antimicrobial and cytotoxic assays. Additionally, our results suggested that talathermophilins might be stimulators of their own growth, and *T. thermophilus* strain YM1-3 cultivated in media containing talathermophilin appeared to grow better than those in media without talathermophilin. Motivated by our previous study, we further investigated the metabolic profiles of 28 thermophilic microorganisms collected from the same habitat as that of *Talaromyces thermophilus* strain YM1-3. We noted that *Talaromyces thermophilus* YM3-4 could yield minute amounts of compounds with UV absorptions at 217, 242, and 309 nm.[3] Detailed chemical study of a scale-up culture of this strain led to the discovery of a series of indole alkaloids with different prenylated patterns. Their structures were elucidated through extensive NMR and MS analyses. Compounds **1** and **2** were

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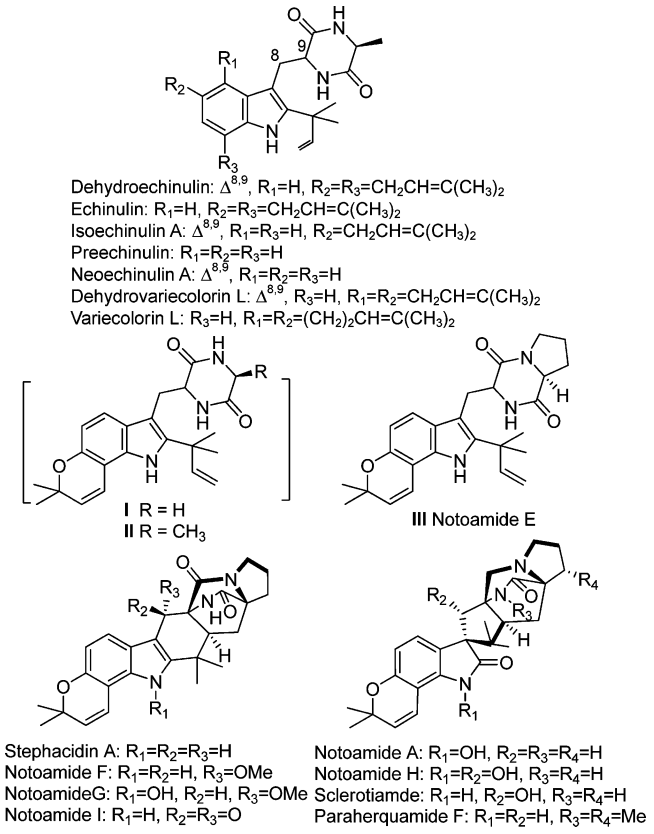

Figure 1. Representative prenylated tryptophan derived alkaloids isolated from fungi. The arrangement is according to the hypothetical biosynthetic processing level. Structures in brackets have not been obtained as natural products.

determined to be identical with the two putative biosynthetic intermediates **I** and **II**. Compound **3** was identified as a new simple prenylated indole alkaloid, and for the first time cyclo(glycyltryptophyl) (**4**) was isolated as a naturally occurring metabolite. Talathermophilins A and B (**5** and **6**) were also isolated from the same *T. thermophilus* strain YM3-4. Thus, a biosynthetic pathway accommodating these biosynthetic intermediates for pyranoindole alkaloids derived from glycine and alanine could be postulated.

The molecular formula of **1** was determined to be $C_{23}H_{27}N_3O_3$ on the basis of its high-resolution ESI mass spectrum. Strong UV absorptions at 217, 242, and 310 nm were indicative of the presence of a conjugated system in **1**. The IR spectrum of **1** showed absorption bands for NH (3381 cm^{-1}), C=O (1679 cm^{-1}), and aromatic functionalities (1641 and 1450 cm^{-1}) in the molecule. The ^1H NMR spectrum of **1** recorded in CD_3OD (Table 1) exhibited signals attributable to five olefinic methines (δ_H 7.26, 6.97, 6.51, 6.24, 5.66), one olefinic methylene (δ_H 5.14 and 5.10), and four methyl groups (δ_H 1.55, 1.54, 1.40, 1.39, each 3H). The ^{13}C NMR and DEPT spectra of **1** displayed signals for 23 carbon atoms, corresponding to 4 methyls, 2 methylenes, 1 methine, 1 quaternary carbon, 1 oxygenated quaternary carbon, 5 aromatic methines, 1 olefinic methylene, 6 aromatic quaternary carbons, and 2 lactam carbonyl groups. All the above data indicated the presence of a tetrasubstituted indole core, a diketopiperazine moiety, and two isoprenyl groups. Comparison of the ^1H and ^{13}C NMR data of **1** with those of talathermophilin A (**5**) demonstrated that these two compounds shared the same skeleton and the only difference was that **1** lacked a double bond between C15 and C16. The NOE correlations of H-4 (δ_H 7.26) with H-16 (δ_H 4.14) in the NOESY spectrum of **1** indicated the conformation of the diketopiperazine, as shown in Figure 2.

The ESIMS of **2** indicated a molecular formula of $C_{24}H_{29}N_3O_3$, which had one more CH_2 unit than **1**. The UV and IR spectra of **2** were almost identical with those of **1**, suggesting structural properties similar to those of **1**. The ^1H and ^{13}C NMR data of the two compounds were also very similar. The only difference between them was that the methylene group (δ_C 45.4; δ_H 3.65) in **1** was replaced by a methine group (δ_C 52.1; δ_H 3.93) and a methyl group (δ_C 21.1; δ_H 1.28) in **2**. All the above data suggested that compound **2** was the C-19 methylated analogue of **1**. Further comparison of the ^1H and ^{13}C NMR data of **2** with those of talathermophilin B (**6**) demonstrated that **2** differed from **6** only in the disappearance of the double bond between C15 and C16.

Unambiguous assignments of the NMR data of **1** and **2** were achieved through 2D NMR (^1H–^1H COSY, HSQC, HMBC, and ROESY) experiments. The structures of **1** and **2** are closely related to that the recently reported intermediate **III**, notoamide E,[3] and are identical with the putative biosynthetic intermediates **I** and **II**, which were derived from a glycine and an alanine, respectively.[6] The optical rotations of **1** and **2** were negative, as was that of notoamide E: $[\alpha]_D^{20} = -28°$ (*c* 0.013, MeOH).[3] Compounds **1** and **2** were then identified as (*S*)-3-((1,7-dihydro-7,7-dimethyl-2-(2-methylbut-3-en-2-yl)pyrano-[2,3-*g*]indol-3-yl)methyl)piperazine-2,5-dione and (3*S*,6*S*)-3-((1,7-dihydro-7,7-dimethyl-2-(2-methylbut-3-en-2-yl)pyrano-[2,3-*g*]indol-3-yl)methyl)-6-methylpiperazine-2,5-dione (Figure 2), respectively, and named talathermophilins C and D.

The ESIMS of **3** revealed a molecular formula of $C_{18}H_{21}N_3O_2$, indicating it contains one less C_5H_6O unit than **1**. Comparison of the ^1H and ^{13}C NMR data of **3** with those of **1** demonstrated that a simple indole core in **3** took the place of the pyranoindole core in **1**. Further comparison of the NMR data of **3** with those of the known prenylated tryptophan alkaloid preechinulin revealed that **3** was a C-19 demethylated analogue of preechinulin.[7] Thus, **3** was established as (*S*)-3-((2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)methyl)piperazine-2,5-dione (Figure 2) and was named talathermophilin E.

Compound **4** was established as cyclo(glycyltryptophyl) according to the similarity of its NMR data with those of the previously reported synthetic product.[8] A literature survey indicated that this is the first time compound **4** was reported as a natural product.

On the basis of the available data, we proposed the biosynthetic pathways of these precursors as illustrated in the Supporting Information, which could well accommodate the formation of all relevant metabolites. Since production of two related nonribosomal peptides from a single NRPS is commonplace,[9] the structures of **1** and **2** were sufficiently similar to suggest that they could stem from one common biosynthetic pathway.

The biosynthesis of **1** and **2** possibly involved similar levels of assembly and enzyme-catalyzed selective C–H oxidation reactions as encountered in notoamide E.[2g] A likely scenario for the biogenesis of **1** is thought to start from **4**, followed by reverse prenylation at C-2 of the indole to form **3**. From here on, 2,2-dimethyl-2*H*-pyran derived from the second isoprene building block is constructed to give **1**.

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Table 1. ^{1}H (400 MHz, CD_3OD) and ^{13}C NMR (100 MHz) Data of 1, ^{1}H (600 MHz, CD_3OD) and ^{13}C NMR (150 MHz) Data of 2 and 4, and ^{1}H (500 MHz, C_5D_5N) and ^{13}C NMR (125 MHz) Data of 3

	1[a]		2[a]		3[a]		4[a]	
no.	δ_C, type	δ_H (J, Hz)	δ_C	δ_H (J, Hz)	δ_C	δ_H (J, Hz)	δ_C	δ_H (J, Hz)
1						11.3, br s		
2	142.3, C		142.3		142.6	7.18 (overlap)	126.1	7.06, s
3	105.7, C		105.9		106.0		109.0	
4	119.2, CH	7.26, d (8.4)	119.2	7.24, d (8.4)	119.4	7.95, d (7.8)	120.2	7.59, d (8.2)
5	110.8, CH	6.51, d (8.4)	110.8	6.52, d (8.4)	118.9	7.20, d (overlap)	119.7	7.08, t (7.1)
6	149.6, C		149.6		121.5	7.15 (overlap)	122.6	7.00, t (7.1)
7	106.3, C		106.4		111.3	7.34, d (8.0)	112.2	7.33, d (8.4)
8	133.1, C		133.1		136.2		137.9	
9	125.3, C		125.3		130.0		128.8	
10	40.6, C		40.5		39.6			
11	148.3, CH	6.24, dd (10.5, 17.3)	148.3	6.23, dd (10.5, 17.4)	147.2	6.35, dd (10.5, 17.4)		
12	111.7, CH_2	5.14, d (17.3)	111.9	5.14, d (17.4)	111.2	5.18, d (17.4)		
		5.10, d (10.5)		5.10, d (10.5)		5.12, d (10.5)		
13	28.7, CH_3	1.55, s	28.9	1.56, s	28.4	1.59, s		
14	28.6, CH_3	1.54, s	28.7	1.56, s	28.4	1.56, s		
15	31.0, CH_2	3.40, dd (14.6, 4.3)	32.0	3.46, dd (14.7, 4.1)	31.5	3.90, dd (14.2, 2.8)	31.2	3.13, dd (15.0, 3.9)
		3.38 dd (14.6, 8.4)		3.35, dd (14.7, 9.4)		3.68, dd (14.2, 11.0)		2.49, d (15.0)
16	57.5, CH	4.14, dd (8.4, 4.3)	57.2	4.22, dd (9.4, 4.1)	57.3	4.75, br d (10.8)	57.5	4.14, s
17	171.4, C		170.1		169.6		171.1	
18						9.22, br s		
19	45.4, CH_2	3.67, d (18.1)	52.1	3.93, q (6.8)	45.7	4.36, d (17.1)	44.8	3.47, d (15.0)
		3.63, d (18.1)				4.24, d (17.1)		3.45, d (15.0)
20	168.7, C		170.7		166.6		168.9	
21						9.28, br s		
22	119.3, CH	6.97, d (9.7)	119.4	6.98, d (9.7)				
23	130.0, CH	5.66, d (9.7)	130.0	5.66, d (9.7)				
24	76.5, C		76.4					
25	27.7, CH_3	1.40, s	27.6	1.40, s				
26	27.6, CH_3	1.39, s	27.6	1.40, s				
27			21.1	1.28, d (7.0)				

[a]Signal partially obscured.

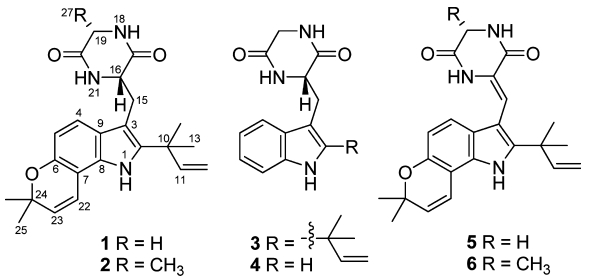

Figure 2. Tryptophan alkaloids from *T. thermophilus* YM3-4.

We were unable to demonstrate the prenylation of brevianamide F, i.e., cyclo-L-prolyl-L-tryptophan,[10] by *T. thermophilus* YM3-4 to provide notoamide E.

In conclusion, we have identified four compounds which may be precursors of the postulated biosynthetic pathways for talathermophilins from the thermophilic fungus *T. thermophilus* YM3-4, using chemical screening of metabolite profiles of 28 thermophilic microorganisms. This discovery validates thermophilic fungi as a potential source of novel natural products with interesting structures, which could complement the metabolite libraries of fungi living at a common temperature.

EXPERIMENTAL SECTION

General Experimental Procedures. Silica gel 60 (Merck, 200–400 mesh) was used for column chromatography. Column chromatography was performed on 200–300 mesh silica gel (Qingdao Marine Chemical Factory, People's Republic of China). Optical rotations were measured on a Horiba-SEAP-300 spectropolarimeter. UV spectral data were obtained on a Shimadzu 210A double-beam spectrophotometer. IR spectra were recorded on a Bruker Tensor-27 spectrometer with KBr pellets. NMR experiments were carried out on either a Bruker AV-400 or a DRX-500 spectrometer with TMS as internal standard. MS were recorded on a VG Auto-Spec-3000 spectrometer. High-resolution ESIMS data were measured on a Bruker Bio-TOF III electrospray ionization mass spectrometer. The TLC spots were detected by spraying the TLC plates with 20% (w/v) H_2SO_4 and then heating them on a hot plate.

Fungal Material. The thermophilic fungus strain YM3-4 was collected in Tengchong hot springs, Yunnan Province, People's Republic of China, in November 2004, and identified as *Talaromyces thermophilus* by the morphological features, including the conidiophores, the submerged hyphae, and rates of growth. This identification was supported by sequence analysis of the internal transcribed spacers (ITS) of the rDNA as described in the previous report.[11] The isolate was deposited as YM3-4 in the strain collection of Laboratory for Conservation and Utilization of Bio-Resources & Key Laboratory for Microbial Resources of the Ministry of Education, Yunnan University. After the conidia had developed on PDA slants in test tubes at 45 °C, the strain was kept at −30 °C as a stock culture.

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Extraction and Isolation. A 40 L portion of fermentation broth of YM3-4 was filtered to separate the mycelia from the culture. The culture filtrate was concentrated in vacuo and partitioned with ethyl acetate (1200 mL × 5), and the organic fraction was evaporated to dryness to give 13 g of residue. This gum was loaded onto a macroporous resin column and eluted with H_2O/MeOH with decreasing polarity to yield eight fractions based on TLC behavior. Fraction C (2.4 g) obtained on elution with 50−90% MeOH/H_2O was further subjected to a Sephadex LH-20 gel column with MeOH as eluent to yield five subfractions. Subfraction 4 was chromatographed on a silica gel column with $CHCl_3$/MeOH (30/1) as eluent to yield **2** (33 mg). Fraction F (0.7 g) was subjected to Sephadex LH-20 washing with MeOH to yield six subfractions. Subfraction 4 (0.5 g) was subjected to Sephadex LH-20 washing with acetone to give **3** (45 mg). Subfraction 5 was rechromatographed over Sephadex LH-20 with with acetone as eluent to afford **5** (16 mg) and **6** (9 mg). Fraction G (0.4 g) was subjected to Sephadex LH-20 washing with MeOH to yield four subfractions. Subfraction 2 (0.08 g) was repeatedly subjected to silica gel column with petroleum ether/acetone (4/1) as eluent to yield **1** (16 mg). By the same means, subfraction 3 (0.08 g) was repeatedly subjected to silica gel column with petroleum ether/acetone (3/1) as eluent to yield **4** (11 mg).

Brevianamide F in *T. thermophilus* YM3-4. Two disks of 3 cm^2 diameter of *T. thermophilus* YM3-4 cultured on a PDA plate at 45 °C for 30 days were added into a 500 mL flask containing 250 mL of PDB medium, and then the flasks were cultivated in a shaker (180 rpm) at 45 °C. On the third day, Brevianamide F (3 mg) was added into the flask. The flask was incubated in the shaker (180 rpm) at 45 °C for 30 days. The fermentation broth was filtered and concentrated under reduced pressure. A 10 μL sample of the extracts was used for analysis by HPLC-DAD. At a flow rate of 1 mL/min, the sample was injected onto a ZORBAX SB-C_{18} column (5 μm, 4.6 × 250 mm) (Agilent, USA). The compounds were detected at 347 nm, and their retention times, UV spectra, and peak areas were compared with those of authentic compounds.

*Talathermophilin C (**1**):* yellow powder; $[\alpha]_D^{23.5}$ = −4.79° (*c* 0.1, MeOH); UV (MeOH): λ_{max} (log ε) 217.2 (4.45), 242.2 (4.54), 309.6 (4.01) nm; IR (KBr) ν_{max} 3381, 2968, 2928, 2874, 2854, 1679, 1641, 1450, 1379, 1358, 1322, 1288, 1251, 1216, 1190, 1164, 1121, 1074, 1042, 999, 919, 803, 783, 740 cm^{-1}; HRESI-MS *m/z* (positive) 394.2154 $[M + H]^+$, (negative) 392.2075 $[M - H]^-$ (calcd for $C_{23}H_{26}N_3O_3$ 392.2078).

*Talathermophilin D (**2**):* yellow powder; $[\alpha]_D^{23.5}$ = −45.01° (*c* 0.1, MeOH); UV (MeOH): λ_{max} (log ε) 217.6 (4.31), 241.8 (4.35), 309.4 (3.83) nm; IR (KBr) ν_{max} 3384, 2966, 2927, 2873, 2856, 1725, 1678, 1641, 1450, 1379, 1327, 1249, 1217, 1191, 1167, 1122, 1066, 919, 805, 772, 739, 582, 435 cm^{-1}; HRESI-MS (positive) 408.2303 $[M + H]^+$, (negative) 406.2227 $[M - H]^-$ (calcd for $C_{24}H_{28}N_3O_3$ 406.2230).

*Talathermophilin E (**3**):* yellow powder; $[\alpha]_D^{23.5}$ = +5.20° (*c* 0.1, AcOH); UV (MeOH): λ_{max} (log ε) 223.7 (4.52), 283.6 (3.95), 292.4 (3.83) nm; IR (KBr) ν_{max} 3384, 2967, 1670, 1655, 1379 cm^{-1}; HRESI-MS (negative) 310.1426 $[M - H]^-$ (calcd for $C_{18}H_{20}N_3O_2$, 310.1430).

*Cyclo(glycyltryptophyl) (**4**):* yellow powder; $[\alpha]_D^{23.5}$ = +12.80° (*c* 0.1, AcOH); HRESI-MS (positive) 266.0920 $[M + Na]^+$ (calcd for 266.0923 $C_{13}H_{11}N_3O_2Na$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving spectroscopic data of compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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