Furan Metabolites from the Sponge-Derived Yeast *Pichia membranifaciens*

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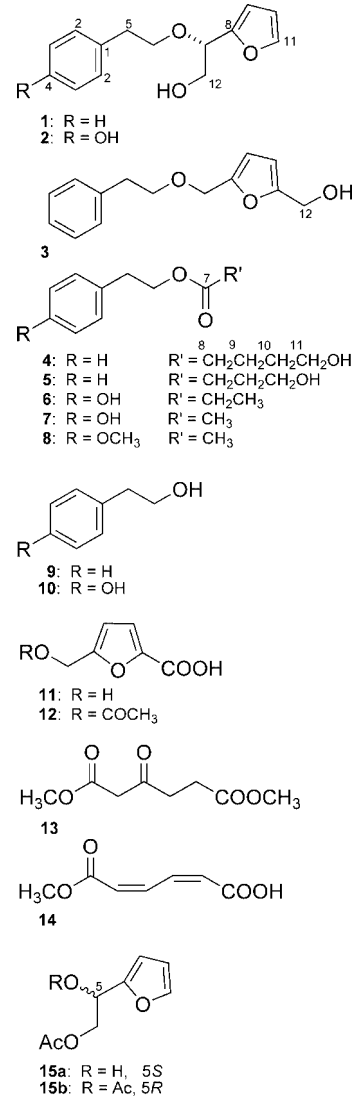
Five new compounds, pichiafurans A−C (**1**–**3**) and pichiacins A and B (**4** and **5**), along with five known compounds (**6**–**10**), have been isolated from the yeast *Pichia membranifaciens* derived from a marine sponge *Petrosia* sp. Their structures were elucidated by 1D and 2D NMR and mass spectrometry techniques. Pichiafurans are rare examples of monofurano metabolites isolated from yeast.

Marine microorganisms have become an important source of pharmacologically active metabolites. Recently, marine microorganisms have proven to produce a variety of chemically interesting and biologically significant secondary metabolites, and some of them are expected to serve as lead compounds for drug development.[1,2] The genus *Pichia*, which comprises 91 species,[3] currently represents one of the largest yeast genera. Yeasts of this genus are widely distributed and can be found in natural habitats such as soil, fresh water, tree exudates, insects, plants, and fruits and also as contaminants in a variety of foods and beverages, including juices and soft drinks, alcoholic beverages, and high-sugar-containing products. Some species of this genus have beneficial effects in food; for example, they contribute to the early stages of wine fermentation and in the processing of different types of cheeses.[4,5] However, some species have been reported as human pathogens.[6,7] *Pichia membranifaciens* has not been previously isolated from any marine source. Although the production of 1,3-dihydroxyacetone and killer toxin against other yeasts and fungi has been reported from this yeast,[8,9] no chemical studies of its secondary metabolites have been previously conducted, which prompted us to undertake the present work. In continuation of our projects aimed at finding new natural products with cytotoxic activity and/or novel chemical structures from marine organisms and marine-derived microorganisms,[10–13] brine shrimp lethality-guided fractionation of the EtOAc crude extract of *P. membranifaciens* (LD_{50} = 170 μg/mL) yielded 10 metabolites (**1**–**10**). Herein, we report the isolation and structure elucidation of the pichiafurans (**1**–**3**) and pichiacins (**4** and **5**).

The yeast *P. membranifaciens* was separated from a marine sponge *Petrosia* sp., collected from Jeju Island, South Korea, and cultivated in shake flasks containing PMG medium with 75% sea water. After cultivation for 21 days at 30 °C, the whole broth culture (30 L) was repeatedly extracted with EtOAc. After partition between 90% aqueous MeOH and *n*-hexane, the dried aqueous MeOH-soluble portion was subjected to flash column chromatography over silica followed by preparative reversed-phase HPLC. The separation was guided by ^{1}H NMR monitoring and brine shrimp lethality to yield compounds **1**–**10**.

Pichiafuran A (**1**) was obtained as a colorless oil. Its molecular formula, $C_{14}H_{16}O_3$, was established by HRFABMS ([M + Na]$^+$ at *m*/*z* 255.1019, Δ +2.2 mmu), indicating the presence of seven degrees of unsaturation. The structure of **1** was deduced from 1D (^{1}H, ^{13}C) and 2D (^{1}H–^{1}H COSY, HSQC, and HMBC) NMR data.



The ^{13}C NMR spectrum of **1** (Table 1) revealed only 12 carbon signals; however, two showed very high intensities at δ_C 129.9 and 129.3, indicating the existence of four overlapping signals. Ten of these signals were assigned for sp^2 hybridized carbons [δ_C 153.9, 143.7, 140.3, 129.9 (2C), 129.3 (2C), 127.1, 111.1, 109.6], indicating the existence of seven double-bond equivalents. Furthermore, a methylene group at δ_C 37.2, two oxymethylene groups at δ_C 71.3 and 64.7, and an oxymethine group at δ_C 77.6 were observed. The ^{1}H NMR spectrum of **1** (Table 1) contained signals

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Table 1. ^{1}H and ^{13}C NMR Data of Compounds **1**–**3** in CD_3OD[a]

	1[b]		**2**		**3**[b]	
position	δ_C	δ_H	δ_C[c]	δ_H[d]	δ_C	δ_H
1	140.3		130.4		138.9	
2	129.3	7.23 (m)	130.5	6.98 (d, 8.0)	128.6	7.23 (m)
3	129.9	7.17 (m)	115.9	6.66 (d, 8.0)	129.3	7.18 (m)
4	127.1	7.14 (m)	156.7		126.5	7.15 (m)
5	37.2	2.82 (m)	36.4	2.74 (m)	36.4	2.82 (t, 7.0)
		2.79 (m)		2.68 (m)		
6	71.3	3.62 (t, 7.0)	71.5	3.56 (t, 7.0)	71.5	3.65 (t, 7.0)
7	77.6	4.41 (dd, 7.5, 7.5)	77.3	4.40 (dd, 7.5, 7.5)	65.2	4.41 (br s)
8	153.9		153.8		152.1	
9	109.6	6.27 (d, 2.0)	109.3	6.29 (d, 2.0)	110.2	6.23 (d, 3.5)
10	111.1	6.35 (dd, 2.0, 2.0)	110.9	6.35 (dd, 2.0, 2.0)	108.8	6.25 (d, 3.5)
11	143.7	7.45 (d, 2.0)	143.5	7.45 (d, 2.0)	154.2	
12	64.7	3.78 (dd, 7.5, 7.5)	64.5	3.78 (dd, 7.5, 7.5)	57.7	4.46 (br s)
		3.69 (dd, 7.5, 7.5)		3.70 (dd, 7.5, 7.5)		

[a] Multiplicities and coupling constants are in parentheses. [b] ^{1}H and ^{13}C NMR were measured at 400 and 100 MHz, respectively. [c] Assignements are based on HMBC and HSQC spectroscopic data. [d] Measured at 500 MHz.

characteristic of an α-substituted furan [δ_H 7.45 (d, J = 2.0 Hz), 6.35 (dd, J = 2.0, 2.0 Hz), 6.27 (d, J = 2.0 Hz)] and a monosubstituted phenyl group (δ_H 7.23, 7.17, 7.14), plus one methylene group (δ_H 2.84, 2.79), two oxymethylene groups [δ_H 3.78 (1H, dd, J = 7.5, 7.5 Hz), 3.69 (1H, dd, J = 7.5, 7.5 Hz); 3.62 (2H, t, J = 7.0 Hz)], and an oxymethine group at δ_H 4.41 (dd, J = 7.5, 7.5 Hz). The connection between C-6 and C-7 through oxygen was confirmed on the basis of HMBC correlations from H_2-6 (δ 3.62) to C-7 (δ 77.6) and vice versa. The HMBC correlations from H-5 (δ 2.82) to C-1 (δ 140.3) and H-7 (δ 4.41) to C-8 (δ153.9) were also observed (Figure 1). The configuration at C-7 was proposed to be *S* by comparison of the optical rotation [**1**: $[\alpha]^{26}_D$ −27.0 (*c* 0.05 in CH_2Cl_2), $[\alpha]^{26}_D$ −64.4 (*c* 0.15 in MeOH)] with those of model compounds **15a** and **15b**. Negative optical rotation was reported for the synthetic model compound **15a** (5*S* configuration), $[\alpha]_D$ −22.3 (*c* 2.61 in CH_2Cl_2), and that for **15b** (5*R* configuration) was positive, $[\alpha]_D$ 107.7 (*c* 1.90 in CH_2Cl_2).[14] Thus, the chemical structure of **1** was established as (7*S*)-2-(furan-2-yl)-2-(phenethyloxy)ethanol.

Pichiafuran B (**2**) was obtained as a colorless oil. Its molecular formula was established as $C_{14}H_{16}O_4$ on the basis of HRFABMS and NMR data. The exact mass of the $[M + Na]^+$ ion (*m*/*z* 271.0949) matched well with the expected molecular formula $C_{14}H_{16}O_4Na$ (Δ +0.3 mmu), which was 16 mass units higher than **1**. The ^{1}H NMR spectrum of **2** was basically the same as that of **1**, except for slight differences in the aromatic region (Table 1). The presence of only two signals (δ 6.98/H_2-2 and 6.66/H_2-3) for the phenyl group suggested it to be 1,4-disubstituted. An examination of the ^{13}C signals in this region [δ_C 156.7, 130.5 (2C), 130.4, and 115.9 (2C)] indicated the presence of a terminal *para*-hydroxybenzene moiety in **2** instead of the phenyl group found in **1**. This was further supported by a gradient HMBC experiment, which showed correlations from both H-2 (δ 6.98) and H-3 (δ 6.66) to C-1 (δ 130.4) and C-4 (δ 156.7). The 7*S* configuration in **2** was determined on the basis of optical rotation data [**2**: $[\alpha]^{25}_D$ −12.0 (*c* 0.05 in MeOH); **1**: $[\alpha]^{26}_D$ −64.4 (*c* 0.15 in MeOH)]. Thus, the structure of pichiafuran B (**2**) was determined to be the 4-hydroxy derivative of pichiafuran A (**1**).

Pichiafuran C (**3**) was also obtained as a colorless oil. The HRFABMS of **3** supported the molecular formula $C_{14}H_{16}O_3$, the same as **1**. The exact mass of the $[M + Na]^+$ ion (*m*/*z* 255.1012) matched well with the expected molecular formula, $C_{14}H_{16}O_3Na$ (Δ +1.5 mmu). Comparison of the NMR spectra showed that the ^{1}H and ^{13}C NMR data of **3** (Table 1) were similar to those of **1**. The major differences were the presence of an α-disubstituted furan moiety in **3** (δ_C 154.2, 152.1, 110.2, and 108.8) instead of an α-monosubstituted furan in **1** (δ_C 153.9, 143.7, 111.1, and 109.6) and an upfield-shifted oxymethylene group (δ_C 57.7, **1**: δ_C 64.7). HMBC correlations from H-9 (δ 6.23) to C-8 (δ 152.1), C-10 (δ 108.8), and C-11 (δ 154.2) and from H-10 (δ 6.25) to C-9 (δ 110.2), C-8 (δ 152.1), and C-11 (δ 154.2) confirmed the existence of the α-disubstituted furan moiety in **3**. Moreover, HMBC correlations observed from H_2-6 (δ 3.65) to C-7 (δ 65.2) as well as from H_2-7 (δ 4.41) to C-6 (δ 71.5), C-8 (δ 152.1), and C-9 (δ 110.2) clearly showed the attachment of the α-disubstituted furan at C-7. Additional long-range correlations from H-10 (δ 6.25) to C-12 (δ 57.7) and from H_2-12 (δ 4.46) to C-11 (δ 154.2) and C-10 (δ 108.8) justified the placement of the oxymethylene functionality at C-11 (Figure 1).

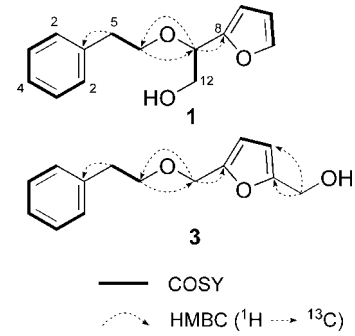

Figure 1. Key COSY and HMBC correlations of pichiafurans A (**1**) and C (**3**).

The molecular formula of pichiacin A (**4**), isolated as a colorless oil, was assigned as $C_{13}H_{18}O_3$ on the basis of HRFABMS ($[M + Na]^+$ at *m*/*z* 245.1180, Δ +2.6 mmu) and the results of ^{1}H and ^{13}C NMR spectroscopic interpretations. The ^{13}C spectrum of **4** showed four sp^3 methylene groups at δ_C 35.7, 33.4, 31.6, and 21.2, two oxymethylene carbons at δ_C 65.8 and 61.8, and five sp^2 carbons, including one ester carbonyl carbon at (δ_C 175.4). The presence of a monosubstituted phenyl group was indicated by the ^{1}H NMR signals at δ_H 7.26, 7.21, and 7.19 and confirmed by resonances at δ_C 139.2, 129.7, 129.2, and 127.3 in the ^{13}C NMR spectrum. On the other hand, from detailed investigation of the data from HSQC, HMBC, and ^{1}H−^{1}H COSY experiments, it was possible to develop the structure of the linear part from C-5 through C-11. The attachment of the linear part to the aromatic moiety was established by correlations observed in the HMBC from H_2-5 (δ 2.93) to C-1 (δ 139.2) and C-2 (δ 129.2) and from H-2 (δ 7.26) to C-5 (δ 35.7).

Pichiacin B (**5**), obtained as a yellow oil, showed the molecular formula $C_{12}H_{16}O_3$, as deduced from the HRFABMS ($[M + Na]^+$ at *m*/*z* 231.0991, Δ −0.6 mmu), which was 14 mass units less than **4**. Comparison of the NMR spectra of **5** and **4** showed that the ^{1}H, HSQC, HMBC, and ^{1}H–^{1}H COSY NMR spectra of **5** were almost superimposable to those of **4**. The only difference was the absence

of one methylene group in the linear part in **5**, which was also in accordance with the decreased mass.

Compounds **6**–**10** were identified by comparison of their data with those reported for these known compounds. Compound **6** is known as a synthetic product,[15] whereas compound **7** has previously been reported from olive oil.[16] Compound **8** was isolated from essential oil of *Narcissus* varieties,[17] and compound **9** was reported as a volatile substance produced by the ligninolytic fungus *Phlebia radiata*[18] and also found in several apple cultivars.[19] Tyrosol (**10**) has previously been reported from olive oil as well.[16,20]

Compounds **1**−**3**are rare examples of monofurano metabolites isolated from a yeast. Sumiki's acid (**11**) and acetyl Sumiki's acid (**12**), isolated from the fungus *Cladosporium herbarum*, derived from the marine sponge *Callyspongia aerizusa*, are the closest relatives.[21] The C_6 monofuran moiety of **1**–**3** is likely derived from a triketide. Triketides such as dimethyl β-ketoadipate (**13**) and the monomethyl ester of *cis*,*cis*-muconic acid (**14**), previously reported from the sponge *Plakortis simplex*, may serve as precursors.[22]

Experimental Section

General Experimental Procedures. Optical rotations were measured with a Jasco P-1020 polarimeter using a 1 dm path length cell. UV spectra were recorded on a UV–vis Shimadzu 1240 spectrophotometer. IR spectra were obtained on a Jasco FT/IR-410 spectrometer. The ^{1}H NMR spectra were recorded at 500 and/or 400 MHz, 2D NMR spectra at 500 MHz, and ^{13}C NMR spectra at 100 MHz using Varian INOVA 500 and Varian UNITY 400 spectrometers. FABMS data were obtained on a JEOL JMS SX-102A spectrometer. HRFABMS data were obtained on a JEOL JMS SX-101A spectrometer. Chemical shifts were reported with reference to the respective solvent peaks and residual solvent peaks (δ_H 3.30 and δ_C 49.0 for CD_3OD) using TMS as an internal standard. HPLC was performed with Shodex C18 M 10E (preparative, 250 × 10 mm i.d., 5 μm, 100 Å) and YMC-Pack CN (preparative, 250 × 10 mm i.d., 5 μm, 120 Å) columns using a Shodex RI-101 detector.

Isolation and Taxonomy of the Yeast Strain. A marine sponge *Petrosia* sp. was collected by scuba diving from waters around Jeju Island during a collection trip in October 2004. After sterilization with 70% aqueous ethanol, the sponge sample was rinsed with sterile H_2O. The sterilized sponge was then cut into pieces and placed on agar plates containing PMG medium: 20 g/L agar, 1 L of water (75% sea water and 25% distilled H_2O), and penicillin-streptomycin solution (cell culture reagent, 10 000 units/mL, 5 mL/L). Fungal and yeast colonies growing out of the sponge tissue were transferred onto new agar plates containing PMG medium for sporulation. The strain (J04J-1)F-9E was identified as *Pichia membranifaciens* on the basis of morphology and biochemical analysis.

Cultivation. The yeast was grown in PMG seawater medium (peptone, 0.1%; malt extract, 2%; and D-glucose, 2%) for 21 days at 30 °C and 145 rpm on a rotary shaker in eight 2 L Erlenmeyer flasks, each containing 1.25 L of liquid medium. These cultures were inoculated with 30% (v/v) of a 7-day preculture (8 flasks, each 300 mL) in the same medium and incubated under the same conditions. The large-scale fermentation was performed in a total volume of 30 L.

Extraction and Isolation. The mass cultivated yeast whole broth culture was exhaustively extracted with EtOAc (3 × 30 L) to yield 5.5 g of a highly viscous brownish material. The residue was redissolved in 90% aqueous MeOH and partitioned with *n*-hexane. The 90% MeOH fraction (3.8 g) was fractionated by flash column chromatography (Si gel 60, 0.015−0.040 mm, Merck) employing gradient elution from $CHCl_3$ to EtOAc to MeOH, to yield 20 fractions (500 mL each). These fractions were evaluated for activity by the brine shrimp lethality assay.[23] Fraction 1 (300 mg) was further fractionated by flash column chromatography using the same previously mentioned conditions to yield 13 subfractions. Subfractions 1-4, 1-5, 1-6, and 1-8 and fractions 3 and 5 were selected for further separation on the basis of ^{1}H NMR monitoring and brine shrimp lethality (these fractions displayed toxicity with an LD_{50} higher than 200 μg/mL).

Compounds **1** (1.8 mg) and **7** (0.4 mg) were obtained by purification of subfraction 1-4 by ODS HPLC, eluting with a solvent system of 50% aqueous MeOH. Using the same conditions, compound **2** (0.7 mg) from fraction 3, compounds **3** (0.8 mg) and **6** (0.3 mg) from subfraction 1-6, compounds **4** (4.0 mg), **5** (0.4 mg), and **8** (0.2 mg) from subfraction 1-8, and compound **9** (3.0 mg) from subfraction 1-5 were obtained. Fraction 5 was subjected to MPLC (Si gel 60, 0.015−0.040 mm, Merck) employing gradient elution from $CHCl_3$ to MeOH to afford compound **10** (40.0 mg).

Pichiafuran A (1): colorless oil; $[\alpha]^{26}_D$ −27.0 (*c* 0.05 in CH_2Cl_2), $[\alpha]^{26}_D$ −64.4 (*c* 0.15 in MeOH); UV (MeOH) λ_{max} (log ϵ) 210 (1.64) nm; IR ν_{max} 3339, 1733, 1149, 795, 727, 670, 587 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; LRFABMS *m/z* 255 $[M + Na]^+$; HRFABMS *m/z* 255.1019 $[M + Na]^+$ (calcd for $C_{14}H_{16}O_3Na$, 255.0997).

Pichiafuran B (2): colorless oil; $[\alpha]^{25}_D$ −12.0 (*c* 0.05 in MeOH); UV (MeOH) λ_{max} (log ϵ) 209 (1.21) nm; IR ν_{max} 3265, 1720, 1180, 720, 690 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; LRFABMS *m/z* 271 $[M + Na]^+$; HRFABMS *m/z* 271.0949 $[M + Na]^+$ (calcd for $C_{14}H_{16}O_4Na$, 271.0946).

Pichiafuran C (3): colorless oil; UV (MeOH) λ_{max} (log ϵ) 204 (1.53) nm; IR ν_{max} 3320, 1740, 1170, 725, 672 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; LRFABMS *m/z* 255 $[M + Na]^+$; HRFABMS *m/z* 255.1012 $[M + Na]^+$ (calcd for $C_{14}H_{16}O_3Na$, 255.0997).

Pichiacin A (4): colorless oil; UV (MeOH) λ_{max} (log ϵ) 206 (1.15) nm; IR ν_{max} 2946, 1723,1248, 1149, 790, 737, 670 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.26 (1H, m, H-2), 7.21 (1H, m, H-3), 7.19 (1H, m, H-4), 4.27 (2H, t, J = 7.0 Hz, H-6), 3.53 (2H, t, J = 6.3 Hz, H-11), 2.93 (2H, t, J = 7.0 Hz, H-5), 2.33 (2H, t, J = 7.5 Hz, H-8), 1.63 (2H, m, H-9), 1.51 (2H, m, H-10); ^{13}C NMR (CD_3OD, 100 MHz) δ 175.4 (C-7), 139.2 (C-1), 129.7 (C-3), 129.2 (C-2), 127.3 (C-4), 65.8 (C-6), 61.8 (C-11), 35.7 (C-5), 33.4 (C-8), 31.6 (C-10), 21.2 (C-9); LRFABMS *m/z* 245 $[M + Na]^+$; HRFABMS *m/z* 245.1180 $[M + Na]^+$ (calcd for $C_{13}H_{18}O_3Na$, 245.1154).

Pichiacin B (5): yellow oil; UV (MeOH) λ_{max} (log ϵ) 208 (1.07) nm; IR ν_{max} 2952, 1731,1240, 1151, 762, 745, 691 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.28 (1H, m, H-2), 7.21 (1H, m, H-3), 7.19 (1H, m, H-4), 4.27 (2H, t, J = 7.0 Hz, H-6), 3.52 (2H, t, J = 6.3 Hz, H-10), 2.92 (2H, t, J = 7.0 Hz, H-5), 2.35 (2H, t, J = 7.5 Hz, H-8), 1.76 (2H, m, H-9); ^{13}C NMR (CD_3OD, assignments based on HMBC and HSQC experiments, 500 MHz) δ 175.0 (C-7), 139.2 (C-1), 129.6 (C-3), 129.2 (C-2), 127.1 (C-4), 65.9 (C-6), 61.8 (C-10), 35.8 (C-5), 31.2 (C-8), 28.5 (C-9); LRFABMS *m/z* 231 $[M + Na]^+$; HRFABMS *m/z* 231.0991 $[M + Na]^+$ (calcd for $C_{12}H_{16}O_3Na$, 231.0997).

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