Cytotoxic Furanosesterterpenes from a Marine Sponge *Psammocinia* sp.

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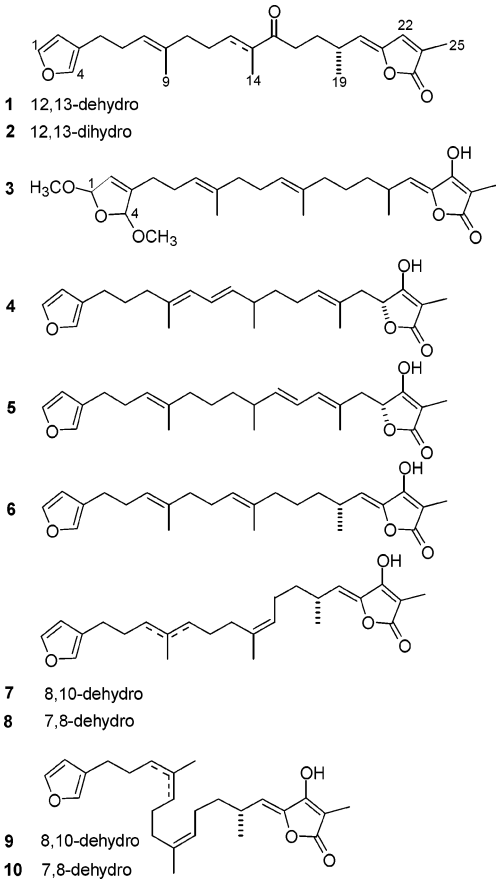
Three new (**1**−**3**) and seven known (**4**−**10**) cytotoxic furanosesterterpenes were isolated from a marine sponge *Psammocinia* sp. by bioactivity-guided fractionation. The structures were established on the basis of NMR and MS analyses. The geometry and absolute configuration were determined on the basis of optical rotation, NMR, and CD data. These compounds were evaluated for cytotoxicity against a small panel of five human tumor cell lines, and most of the compounds showed toxicity to SK-MEL-2. The mixture of compounds **7** and **8** displayed significant inhibition of DNA replication and moderate antioxidant profile.

Marine sponges of the order Dictyoceratida are known to contain various linear furanosesterterpene derivatives that possess interesting biological properties.[1] These linear furanosesterterpenes are characterized by a furan group and a terminal tetronic acid moiety.[2,3] Linear furanosesterterpenes with diverse olefinic regiochemistry are frequently encountered especially in marine sponges of the genera *Ircinia*, *Sarcotragus*, and *Psammocinia* (order Dictyoceratida).[2−11] These furanosesterterpenes displayed a wide range of bioactivity including antiviral, antibacterial, anti-inflammatory, antitumor, and protein phosphatase inhibitory activity and toxicity to sea urchin and starfish eggs.[7,9−12]

In the course of screening for bioactive metabolites from marine sponges collected from Korean waters, we noticed significant activity in the crude extract of *Psammocinia* sp. (order Dictyoceratida). Guided by brine shrimp lethality and ^{1}H NMR monitoring, three new (**1**−**3**) and seven known (**4**−**10**) furanosesterterpenes were isolated. The structures were established on the basis of NMR and MS analyses. The geometry and absolute configuration were determined on the basis of NMR coupling constant, optical rotation, and CD analysis. These compounds were evaluated for cytotoxicity against a small panel of five human tumor cell lines, and most of the compounds showed toxicity to SK-MEL-2. Furthermore, the mixture of compounds **7** and **8** displayed significant inhibition of DNA replication and moderate antioxidant profile. Herein we describe the isolation, structural elucidation, and biological activities of these compounds.

The crude MeOH extract of the frozen marine sponge showed significant activity in the brine shrimp lethality assay (LD_{50}, 126 μg/mL). Guided by this assay, the MeOH extract was further partitioned between H_2O and CH_2Cl_2, followed by partitioning of the CH_2Cl_2 solubles between 90% MeOH (LD_{50}, 9 μg/mL) and *n*-hexane (LD_{50}, 290 μg/mL). The 90% MeOH layer was chromatographed on a reversed-phase flash column with the eluting solvent system of 33 to 0% H_2O/MeOH to afford 20 fractions.



Resultant fractions were further purified by reversed-phase MPLC and HPLC to yield a series of chemically labile sesterterpenes.

Psammocinin A_1 (**1**) was isolated as a light yellow oil. The molecular formula of **1** was established as $C_{25}H_{32}O_4$ on the basis of NMR and MS analyses. In the HRFABMS spectrum, compound **1** showed the $[M + Na]^+$ ion peak at *m*/*z* 419.2181 (calcd for $C_{25}H_{32}O_4Na$, 419.2198). Compound **1** was defined as a linear furanosesterterpene tetronic acid on the basis of the typical ^{1}H and ^{13}C NMR data. A β-substituted furan unit was recognized from the broad singlets at δ_H 7.35, 7.23, and 6.28 in the ^{1}H NMR spectrum (Table 1). The signal at δ_H 7.23 (H-4) was overlapped with

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Table 1. ^{1}H NMR Data of Compounds **1**−**3** (CD_3OD, 500 MHz)

position	1	2	3
1	7.35 (brs)	7.35 (brs)	5.39 (brs)
2	6.28 (brs)	6.28 (brs)	5.66 (brs)
4	7.23 (brs)	7.23 (brs)	5.51 (brs)
5	2.42 (t, 7.5)	2.42 (t, 7.5)	2.20 (m)
6	2.23 (q, 7.5)	2.23 (q, 7.5)	2.20 (m)
7	5.18 (t, 7.5)	5.13 (brt, 7.5)	5.12 (m)
9	1.59 (s)	1.53 (s)	1.60 (s)
10	2.11 (t, 7.5)	1.94 (m)	1.98 (t, 7.5)
11	2.32 (q, 7.5)	1.29 (m)	2.08 (q, 7.5)
12	6.61 (brt, 7.5)	1.52 (m)	5.08 (m)
13		2.52 (m)	
14	1.70 (s)	0.97 (d, 7.0)	1.55 (s)
15			1.94 (m)
16	2.67 (ddd, 16.5, 8.0, 7.0) 2.57 (ddd, 16.5, 8.5, 6.5)	2.45 (m)	1.38 (m)
17	1.78 (dddd, 14.0, 8.0, 7.0, 5.0) 1.60 (dddd, 14.0, 9.2, 8.0, 5.4)	1.74 (dtd, 13.0, 7.5, 5.0) 1.53 (m)	1.35 (m)
18	2.78 (m)	2.77 (m)	2.72 (m)
19	1.08 (d, 7.0)	1.08 (d, 7.0)	1.05 (d, 7.0)
20	5.05 (d, 10.5)	5.07 (d, 10.0)	5.26 (d, 10.0)
22	7.22 (brs)	7.22 (brs)	
25	1.92 (s)	1.93 (s)	1.73 (s)
OCH_3			3.35 (s)
OCH_3'			3.34 (s)

Table 2. ^{13}C NMR Data of Compounds **1**−**3** (CD_3OD, 50 MHz)[a]

position	1	2	3
1	143.8	143.7	109.1
2	111.9	112.0	124.8
3	125.9[b]	125.4[b]	146.5
4	140.0	140.1	108.1
5	25.9	25.9	26.8
6	29.4	29.5	27.4
7	126.0[b]	125.5[b]	125.9
8	135.7	136.3	136.9
9	15.9	15.8	16.1
10	39.2	40.4	40.4
11	28.3	26.3	27.5
12	144.4	33.4	125.5
13	138.0	47.3	135.9
14	11.5	16.6	15.9
15	203.9	216.9	40.6
16	35.8	39.9	26.7
17	33.2	31.6	37.6
18	32.4	32.3	31.8
19	21.1	21.1	21.1
20	120.6	120.5	115.4
21	148.8	149.6	145.3
22	139.7	139.7	165.7
23	130.1	130.2	98.3
24	172.3	172.7	173.8
25	11.4	10.3	6.0
OCH_3			54.21
OCH_3'			54.17

[a] Assignments were supported by HMBC and HSQC experiments. [b] Assignments with the same superscript in the same column may be interchanged.

another olefinic proton signal. This signal was resolved into two olefinic signals at δ_H 7.20 (s, H-4) and 6.95 (s, H-22) in $CDCl_3$. The presence of the 22-deoxytetronic acid moiety (C-21−C-25) was indicated by COSY, HMBC, and HSQC data. The ^{13}C NMR signals at δ_C 148.8 (C-21), 139.7 (C-22), and 130.1 (C-23) were assigned to the 22-deoxytetronic acid moiety (Table 2).[13] No hydroxyl absorption was observed in the IR spectrum. The C-21 (δ_C 148.8) signal displayed HMBC correlations to H-20 (δ_H 5.05) and H-22 (δ_H 7.22), together with very weak correlation to a vinylic methyl signal (H-25, δ_H 1.92). A ^{1}H−^{1}H COSY spectrum

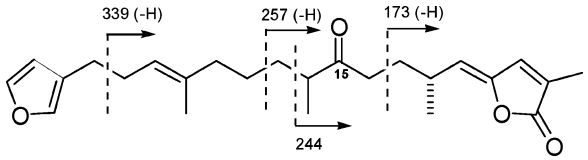

Figure 1. Key fragmentations of the $[M + Na]^+$ ion of **2** in FAB-CID MS/MS.

also showed a correlation between H-22 and H-25. The NMR spectrum featured additional vinylic methyl singlets at δ_H 1.59 (δ_C 15.9), 1.70 (δ_C 11.5), and 1.92 (δ_C 11.4), a secondary methyl doublet at δ_H 1.08 (d, $J = 7.0$ Hz, δ_C 21.1), and trisubstituted olefinic signals at δ_H 5.05, 5.18, and 6.61 (δ_C 120.6, 126.0, and 144.4, respectively). The carbonyl carbon at δ_C 203.9 (C-15) was correlated with a trisubstituted olefinic proton (δ_H 6.61, H-12), a vinylic methyl proton (δ_H 1.70, H-14), and two methylene protons (H-16) in the HMBC spectrum. Thus, the ketone group was apparently located at C-15. The position of double bonds was determined by COSY analysis. The *E* geometry of the trisubstituted double bond (C-7) was deduced on the basis of the upfield resonance (δ_C 15.9, C-9) of the vinylic methyl carbon,[14] and it was further confirmed by the NOE correlation (NOESY) between H-6 and H-9. The geometries of the double bonds at C-12 and C-20 were defined on the basis of the NOE correlations (NOESY) of H-11/H-14 and H-20/H-22. The absolute configuration of C-18 was proposed as *R* on the basis of the positive optical rotation of **1** (+26.9°).[16] Thus, compound **1** was defined as 22-deoxy-15-oxovariabilin and given the trivial name psammocinin A_1.

Psammocinin A_2 (**2**) was isolated as a light yellow oil. The molecular formula of **2** was established as $C_{25}H_{34}O_4$ on the basis of HRFABMS data. Compound **2** also contained a furan unit and a 22-deoxytetronic acid moiety, but showed a rather different ^{1}H NMR spectroscopic pattern from that of **1**. It showed two vinylic methyl singlets (δ_H 1.93 and 1.53) and two secondary methyl doublets (δ_H 1.08 and 0.97) and only two trisubstituted olefinic protons appearing at δ_H 5.07 and 5.13. These trisubstituted olefinic protons were correlated with the methyl carbons at δ_C 15.8 (C-9) and 21.1 (C-19), respectively, in the HMBC spectrum. The position of the double bonds was confirmed by COSY experiment. A carbonyl carbon signal appeared at δ_C 216.9 in the ^{13}C NMR spectrum. This ketone carbonyl group was assumed to be located at C-15 in analogy with the structure of **1**. The carbonyl carbon (C-15) showed long-range correlations with H-13 (δ_H 2.52), H-16 (δ_H 2.45), H-17 (δ_H 1.74 and 1.53), H-12 (δ_H 1.52), and H-14 (δ_H 0.97) in the HMBC spectrum. The position of the ketone group was further corroborated by MS/MS analysis. In the FAB-CID tandem mass spectrum, the fragment ion peaks at *m*/*z* 173, 244, and 257 were supportive of the location of the ketone group at C-15 (Figure 1). The even mass fragment ion at *m*/*z* 244 was determined to be a product of the typical McLafferty rearrangement. For the alternative structure (12-oxo), a different pattern of fragmentation is expected. The absolute configuration at C-18 was assumed to be the same as that of **1**, while the configuration of C-13 remains to be determined.

Psammocinin B (**3**) was isolated as a light yellow oil. The molecular formula of **3** was assigned as $C_{27}H_{40}O_6$ on the basis of combined NMR and MS analyses. The FABMS spectrum of **3** showed the $[M + Na]^+$ ion at *m*/*z* 483. In the ^{1}H NMR spectrum, two methoxyl groups were observed at δ_H 3.35 and 3.34, and an oxygenated furan unit was recognized from the broad singlets at δ_H 5.66, 5.51, and 5.39 (Table 1). In the HMBC spectrum, H-1 at δ_H 5.39 was

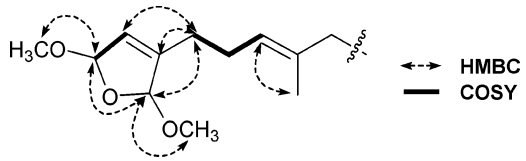

Figure 2. Key HMBC and COSY correlations of **3**.

Table 3. Cytotoxicity Data of Compounds **1**−**10** against Human Solid Tumor Cells[a]

compound	A549	SK-OV-3	SK-MEL-2	XF498	HCT15
1	>30.0	>30.0	7.5	28.1	20.5
2	7.5	12.3	4.8	10.5	11.7
3	8.2	12.6	7.5	7.8	19.2
4	5.2	10.2	4.4	5.1	5.4
5	>30.0	16.5	10.7	10.0	>30.0
6	24.1	18.6	19.0	22.1	23.5
7, **8**	10.5	7.5	5.8	8.7	11.0
9, **10**	>30.0	14.1	14.4	20.3	16.0
doxorubicin	0.03	0.15	0.05	0.15	0.12

[a] Data as expressed in ED_{50} values (μg/mL). A549, human lung cancer; SK-OV-3, human ovarian cancer; SK-MEL-2, human skin cancer; XF498, human CNS cancer; HCT 15, human colon cancer.

correlated with C-2 (δ_C 124.8), C-4 (δ_C 108.1), and the methoxyl group at δ_C 54.21. Also, H-4 at δ_H 5.51 was correlated with C-3 (δ_C 146.5), C-1 (δ_C 109.1), and the methoxyl group at δ_C 54.17 (Figure 2). The data of the tetronic acid moiety, trisubstituted olefinic units, and methyl groups were identical with those of variabilin (compound **6**).[8] The position of the double bonds was determined by comparison of the ^{1}H and ^{13}C NMR data.[8] The correlations of the linear chain were confirmed again from COSY analysis. The geometry of the double bonds was assigned as 7*E* and 12*E* on the basis of the upfield resonances of the vinylic methyl carbons.[14] The 20*Z* geometry was also determined by comparison of the carbon chemical shifts with those reported.[14] The configuration at C-1, C-4, and C-18 remains to be determined. Thus, compound **3** was depicted as a dimethoxy derivative, and possibly an oxygenated artifact, of variabilin, since variabilin is known to be unstable in open air and to produce various autoxidation products.[15]

Compounds **4** and **5** were identified as palinurin and isopalinurin, respectively.[5,18] The configuration at C-21 has not been previously investigated, and it has now been determined on the basis of CD analysis.[10,19] The CD spectrum of **4** showed a negative Cotton effect at 212 nm ($\pi\rightarrow\pi^*$) and a positive Cotton effect at 250 nm ($n\rightarrow\pi^*$), indicating that the absolute configuration of C-21 is *R*. Similarly, the configuration at C-21 of **5** was also defined as *R*. The unconjugated tetronic acid moieties of **4** and **5** were quite labile in the solid state, hence leading to decomposition even at room temperature. Compound **6** was identified as (7*E*,12*E*,18*R*,20*Z*)-variabilin by comparison of NMR data and optical rotation (+41.5°) with those reported.[2,8,20] Compounds **7** and **8** were isolated as an inseparable 1:1 mixture, and they were identified as (8*E*,-13*Z*,18*R*,20*Z*)-strobilinin and (7*E*,13*Z*,18*R*,20*Z*)-felixinin [also known as (7*E*,13*Z*,18*R*,20*Z*)-variabilin[8]], respectively[17,21] Compounds **9** and **10** were also isolated as an inseparable mixture. The major component (**9**) was identified as (8*Z*,13*Z*,18*R*,20*Z*)-strobilinin, and the minor component (**10**) was identified as (7*Z*,13*Z*,18*R*,20*Z*)-felixinin.[14,17]

The compounds (**1**−**10**) were evaluated for cytotoxicity against a small panel of five human solid tumor cell lines, and marginal cytotoxicities were observed (Table 3). These compounds showed slightly selective cytotoxicity against the skin cancer cell (SK-MEL-2). Compounds **2**−**4** and the mixture of **7** and **8** showed a rather higher potency than the others.

Compounds **6**−**10** were the major components of the sponge metabolites, and the mixture of **7** and **8** was further tested for effects on DNA replication and antioxidation. The mixture substantially inhibited SV40 DNA replication in vitro, about 30, 60, and 100% at concentrations of 125, 250, and 500 μM, respectively.[22] The mixture was found to inhibit topoisomerase I and polymerase α-primase, which are involved in DNA replication.[23,24] The IC_{50} value for the polymerase α-primase activity was 5 μM, and topoisomerase I was obviously inhibited at 10 μM. In antioxidant assays, the mixture showed mild scavenging activity on free radical and superoxide anion[25,26] and showed medium inhibitory effect on hydroxyl radical induced DNA breakage.[27]

Experimental Section

General Experimental Procedures. Optical rotations were obtained using a JASCO DIP-370 digital polarimeter. CD spectra were measured using a JASCO J-715 spectropolarimeter (sensitivity 50 mdeg, resolution 0.2 nm). UV spectra were obtained in MeOH, using a Shimadzu mini 1240 UV−vis spectrophotometer. IR spectra were measured by a JASCO FT/IR-410 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC200 and a Varian Inova 500 spectrometer. Chemical shifts were reported with reference to the respective residual solvent or deuterated solvent peaks (δ_H 3.30 and δ_C 49.0 for CD_3OD). FABMS data were obtained on a JEOL JMS-SX-102A double-focusing instrument. HPLC was performed with a YMC ODS-H80 column (preparative, 250 × 20 mm, 4 μm, 80 Å) and a Shodex C18-5E packed column (semipreparative, 250 × 10 mm, 5 μm, 100 Å) using a Shodex RI-71 detector.

Animal Material. The sponge was collected by hand using scuba at a depth of 20 m in October 2001, off Ulleung Island, Korea. The specimen was identified as *Psammocinia* sp. by Prof. C. J. Sim of Hannam University. The sponge was irregular and massive with slight lobes and measured 8.5 × 6.5 and 3.5 cm thick. Oscules, under 1−2 mm in diameter, were scattered on the surface or opened at the top of each lobe. The surface of the body was dark gray, and the interior was dark beige. The texture was elastic and tough. The surface was covered with low and round conules, 1−2 mm high and 2−4 mm apart. The reticulated fiber skeleton was simple and easily broken. Slightly fasciculated primary fibers, 100−300 μm in diameter, were heavily cored with small sand. Secondary fibers, 60−200 μm in diameter, were clear or partially cored with sand. Filaments, 3−5 μm in diameter, emerged from the hole in the fiber. The terminal knob measured 10−12 μm in diameter. A voucher specimen of the sponge (registry No. Spo. 42) was deposited at the Natural History Museum, Hannam University, Daejon, Korea.

Extraction and Isolation. The frozen sponge (4 kg) was extracted with MeOH at room temperature. The MeOH extract was partitioned between H_2O and CH_2Cl_2. The CH_2Cl_2 layer was further partitioned between 90% MeOH and *n*-hexane. The 90% MeOH (21.4 g) fraction was subjected to step gradient reversed-phase flash column chromatography (YMC Gel ODS-A, 60 Å, 500/400 mesh), eluting with a solvent system of 67% → 100% MeOH/H_2O, to afford 20 fractions (Fr.1−Fr.20). These fractions were evaluated for activity in the brine shrimp assay, and fractions Fr.4−Fr.16 were found to be active. The patterns of Fr.9−Fr.12 were similar in TLC. These fractions were combined (6.2 g) and separated again, using the same conditions, to afford 18 fractions (Fr.9-1−Fr.9-18). Fractions Fr.9-12−Fr.9-15 (4.2 g) were combined and were further separated by MPLC (YMC ODS, 60 Å, 400/230 mesh) eluting with 80% → 90% MeOH/H_2O to afford 13 fractions. Guided by the brine shrimp assay, fractions Fr.9-12-8−Fr.9-12-11 (2.5 g) were separated by HPLC (preparative column), eluting with 86%

MeOH/H_2O, to afford **6** (ca. 500 mg), a mixture of **7** and **8** (ca. 500 mg), and a mixture of **9** and **10** (ca. 300 mg). Compounds **4** (11.3 mg) and **5** (3.6 mg) were obtained by purification of fraction Fr.9-12-7 by HPLC (preparative column, 83% MeOH/H_2O). Compounds **1** (3.2 mg) and **2** (4.2 mg) were obtained by purification of Fr.9-11 by HPLC (semipreparative column), eluting with 78% MeOH/H_2O. Compound **3** (4.4 mg) was obtained by purification of fractions Fr.9-12-4−Fr.9-12-6 by HPLC (semipreparative column), eluting with 82% MeOH/H_2O.

Biological Evaluation. The activity of the compounds on the SV40 DNA replication was evaluated as described previously.[22] The reactions ran at 37 °C for 2 h, after which the acid-insoluble radioactivity was measured. The activity of topoisomerase I was measured by the degree of relaxation of the superhelical plasmid DNA.[23] The electrophoresis and photography were done as described previously. DNA polymerase α activity was assayed as described previously.[24] After incubation at 37 °C for 30 min, acid-insoluble radioactivity was determined. The scavenging activity of DPPH radicals was measured according to the method reported.[25] After incubation at room temperature, absorbance (517 nm) of the reaction mixtures was taken after 30 min and 3 h, respectively. The effect on hydroxyl radical induced DNA breakage was performed according to the method of Keum et al.[27] Superoxide anion was generated by xanthine oxidase and detected with the NBT reduction method.[26]

Psammocinin A_1 (1): light yellow oil; $[\alpha]^{21}_D$ +26.9° (*c* 0.12, MeOH); IR (film) ν_{max} 2927, 2865, 1758, 1666, 1442, 1365, 1052, 752 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; FAB-CID MS/MS *m*/*z* 419 $[M + Na]^+$ (100), 338 (1.3), 270 (1.5), 199 (0.9), 173 (0.8), 160 (1.3); HRFABMS *m*/*z* 419.2181 (calcd for $C_{25}H_{32}O_4Na$, 419.2198).

Psammocinin A_2 (2): light yellow oil; $[\alpha]^{21}_D$ +42.1° (*c* 0.18, MeOH); IR (film) ν_{max} 2931, 2861, 1758, 1703, 1446, 1369, 1052, 763 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; FAB-CID MS/MS *m*/*z* 421 $[M + Na]^+$ (100), 339 (0.68), 283 (0.35), 257 (0.64), 244 (0.57), 173 (0.65), 160 (0.49); HRFABMS *m*/*z* 421.2347 (calcd for $C_{25}H_{34}O_4Na$, 421.2355).

Psammocinin B (3): light yellow oil; $[\alpha]^{21}_D$ +16.3° (*c* 0.1, MeOH); ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; FAB-CID MS/MS *m*/*z* 483 $[M + Na]^+$ (100), 451 (15), 326 (20), 173 (30); HRFABMS *m*/*z* 483.2732 (calcd for $C_{27}H_{40}O_6Na$, 483.2723).

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