Hurghadolide A and Swinholide I, Potent Actin-Microfilament Disrupters from the Red Sea Sponge *Theonella swinhoei*

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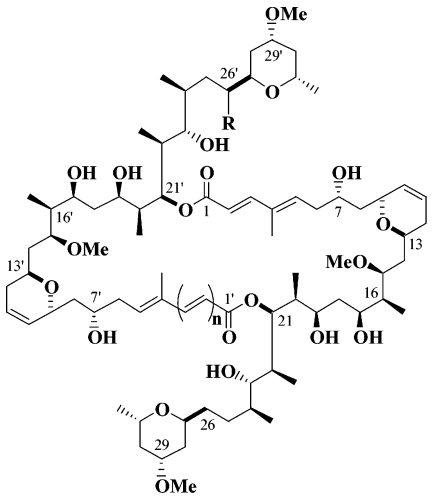
As part of our continuing interest in identifying anticancer drug leads from Red Sea marine organisms, we have investigated the sponge *Theonella swinhoei*. We report here the isolation and structure elucidation of swinholide A (**1**) and two new macrolides, swinholide I (**2**) and hurghadolide A (**3**). Swinholide I is the first derivative of swinholide A with hydroxylation at the side chain. Hurghadolide A possesses an unprecedented asymmetric 42-membered dilactone moiety and presents a novel skeleton of macrolides. The structural determinations were based on extensive interpretation of high-field NMR spectra and HRFABMS data. Swinholide I and hurghadolide A showed in vitro cytotoxicity against human colon adenocarcinoma (HCT-116) with IC_{50} values of 5.6 and 365 nM, respectively. Furthermore, swinholide I and hurghadolide A caused disruption of the actin cytoskeleton at concentrations of 70 and 7.3 nM, respectively. In addition, both compounds were active against *Candida albicans*.

Lithistid sponges are a prominent source of bioactive secondary metabolites, particularly cyclic peptides and macrocyclic bislactones (swinholides).[1] Swinholide A was the first macrolide to be isolated from the Red Sea marine sponge *Theonella swinhoei*.[2] The structure was first assigned as a monomer, revised later to a symmetric cyclic dimer,[3] followed by determination of its absolute stereochemistry.[4] Further investigation of sponges of the genera *Theonella*, *Lamellomorpha*, and *Tedania* led to the identification of isoswinholide A, bistheonellides A (=misakinolide A) and B, a monomeric carboxylic acid of swinholide A, and several swinholide A derivatives, including swinholides B (16′-demethyl), C (29′-*O*-demethyl), D (15′-*O*-demethyl), E (6′-hydroxy), F (2′-*Z* conformer), G (20′-demethyl), and H (7,7′-*O*-dimethyl).[5] More recently, swinholide A and two glycosylated swinholide derivatives, ankaraholides A and B, were reported from two field collections of marine cyanobacteria of the genera *Symploca* and *Geitlerinema*, raising the debate about the real producer of such macrolides in sponges belonging to different genera.[6]

In our ongoing search for new anticancer leads from Red Sea organisms,[7] we have re-examined the sponge *T. swinhoei*. Bioassay-guided separation of the cytotoxic fractions of a MeOH/CH_2Cl_2 extract of a specimen of the marine sponge collected in Hurghada at the Egyptian Red Sea coast resulted in the identification of swinholide A (**1**) and two new potently cytotoxic macrolides, swinholide I (**2**) and hurghadolide A (**3**). Swinholide A possesses a 44-membered symmetric dilactone moiety, while bistheonellide A is a symmetric 40-membered dilactone macrolide. In contrast to both of these compounds, hurghadolide A possesses an unprecedented asymmetric 42-membered dilactone moiety and presents a novel carbon skeleton among this series of macrolides. Furthermore, swinholide I is the first swinholide derivative with hydroxylation on the side chain. Here we present the isolation, characterization, cytotoxicity, and antifungal evaluations of these compounds.

Swinholide A (**1**) was isolated as a light yellow solid. Its structure was deduced from its HRFABMS ($C_{78}H_{132}O_{20}$) data, from 1D (^1H and ^{13}C) and 2D (^1H,^1H-COSY, HMQC, HMBC) NMR spectra (Table 1), and by direct comparison of its chemical shift data with existing literature values.[2−4]



1 = Swinholide A (n = 1, R = H)

2 = Swinholide I (n = 1, R = OH)

3 = Hurghadolide A (n = 0, R = H)

Swinholide I (**2**) displayed a molecular formula of $C_{78}H_{132}O_{21}$ (HRFABMS), being larger than that of swinholide A (**1**) by 16 mass units, corresponding to an additional oxygen atom in the molecule. In contrast to **1**, the ^1H and ^{13}C NMR spectra of **2** (Table 1) displayed additional resonances at δ 3.96/72.0, corresponding to H-26′/C-26′, respectively. This finding was supported by extensive study of the ^1H, ^{13}C NMR, ^1H,^1H-COSY, HMQC, and HMBC spectra. The position of the extra OH moiety at C-26′ was assigned from HMBC correlations of H_2-25′/C-26′, H_2-28′/C-26′, H_3C-24′/C-25′, H_2-28′/C-30′, and H_3C-31′/C-29′ (Figure 1). Furthermore, the assignment of all ^1H and ^{13}C NMR resonances in **2** was supported from interpretation of ^1H, ^{13}C NMR, ^1H,^1H-COSY, HMQC, and HMBC spectra. The presence of an additional OH moiety at C-26 in half of the dimeric molecule resulted in twinning of the ^{13}C resonances of C-22, C-23, C-25, C-28, C-30, C-31, and Me-31 and the ^1H resonances of H_2-25, H_2-30, and Me-31, respectively (Table 1), without any effect on the signals of the dilactone ring skeleton. This observation supported the conclusion that swinholide I was 26′-hydroxy swinholide A and represents the first derivative of swinholide A with oxygenation at the side chain.

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Table 1. ^{1}H and ^{13}C NMR Data for Compounds **1**−**3** in $CDCl_3$ (δ in ppm, J in Hz)

		1[a]		**2**[a]		**3**[a]	
position	mult.	$\delta_C/\delta_{C'}$	$\delta_H/\delta_{H'}$	$\delta_C/\delta_{C'}$	$\delta_H/\delta_{H'}$	$\delta_C/\delta_{C'}$	$\delta_H/\delta_{H'}$
1/1′	qC	170.0		170.0		170.3/170.4	
2/2′	CH	113.2	5.79, d (15.5)	113.3	5.78, d (15.5)	113.5/ −[c]	5.78, d (15.6)/ −[c]
3/3′	CH	153.2	7.58, d (15.5)	153.1	7.57, d (15.5)	153.2/ −[c]	7.60, d (15.6)/ −[c]
4/4′	qC	134.2		134.2		134.3/127.5	
4/4′-Me	CH_3	12.3	1.88, s	12.2	1.80, s	12.3/12.6	1.81, s/1.97, s
5/5′	CH	142.2	6.08, dd (9.0, 5.0)	142.1	6.07, dd (9.0, 5.0)	142.6/144.3	6.05, dd (10.0, 4.3)/7.03, t (6.2)
6/6′	CH_2	37.4	2.46, m	37.4	2.45, m	37.2/37.1	2.46, m
			2.18, m		2.17, m		2.17, m
7/7′	CH	66.6	4.14, t (10.0)	66.6	4.13, t (10.0)	66.7/66.1	4.13, t (10.5)/4.25, t (10.5)
8/8′	CH_2	40.8	1.73, m, 1.58, m	40.8	1.64, m, 1.56, m	40.8/40.7	1.66, m, 1.50, m
9/9′	CH	65.7	4.51, brd (9.1)	65.8	4.51, d (10.8)	67.6	4.50, d (9.7)
10/10′	CH	129.8	5.69, brd (10.3)	129.8	5.69, d (10.4)	129.9/129.7	5.64, d (10.3/5.67, d (10.3)
11/11′	CH	123.2	5.78, brd (10.3)	123.2	5.76, d (10.4)	122.9/123.7	5.71, m/5.75, m
12/12′	CH_2	29.9	2.27, brd (17.5)	29.9	2.26, d (17.5)	29.7	2.35, brd (17.5)
			1.82, m		1.85, m		1.82, m
13/13′	CH	65.8	3.86, m	65.8	3.87, m	64.6	4.50, m
14/14′	CH_2	33.8	2.14, m	33.8	2.13, d (10.7)	34.9	1.94, m
			1.46, m		1.45, t (12.3)		1.53, m
15/15′	CH	75.1	4.01, m	75.2	3.98, m	76.5	3.92, m
15/15′-OMe	CH_3	57.4	3.35, s	57.4	3.35, s	57.1/57.4	3.35, s/3.33, s
16/16′	CH	41.0	1.68, m	41.3	1.65, m	41.6/41.7	1.50, m/1.56, m
16/16′-Me	CH_3	9.4	0.81, d (6.7)	9.3	0.80, d (6.7)	9.4	0.80, d (6.7)
17/17′	CH	73.8	3.83, dd (9.5, 9.5)	73.8	3.82, t (9.5)	73.8/73.9	3.74, m
18/18′	CH	38.4	1.62, m	38.4	1.62, m	37.9/38.0	1.56, m
19/19′	CH	71.3	3.98, m	71.3	3.98, m	70.6/71.1	3.77, m
20/20′	CH	41.3	1.75, dq (10.0, 7.0)	40.8	1.64, m	40.3/40.4	1.70, m
20/20′-Me	CH_3	9.2	0.97, d (7.0)	9.2	0.96, d (6.7)	9.3/9.2	0.96, d (7.0)/0.95, d (7.0)
21/21′	CH	74.3	5.36, d (10.7)	74.3	5.34, d (10.5)	74.6/74.7	5.34, d (10.7)/5.21, d (10.7)
22/22′	CH	37.6	1.95, m	37.6/38.0	1.87, d (12.7)	37.5/37.7	2.00, m/2.46, m
22/22′-Me	CH_3	9.1	0.84, d (7.0)	9.1	0.82, d (7.0)	9.2/9.1	0.85 d (7.0)/0.84 (d, 7.0)
23/23′	CH	76.0	3.12, d (9.5)	76.0/76.1	3.11, d (9.5)	75.9/76.7	2.96, d (9.5)/3.08, d (9.5)
24/24′	CH	33.2	1.65, m	33.2	1.63, m	33.2	1.62, m
24/24′-Me	CH_3	17.7	0.99, d (7.0)	17.7	0.99, d (7.0)	17.6	0.96, d (7.0)/0.95, d (7.0)
25/25′	CH_2	23.9	1.38, m, 1.27, m	23.9/24.1	1.37, m, 1.26, m	23.7/24.0	1.23 m
26/26′	CH_2/	29.3	1.90, m,	29.6/72.0[b]	1.85, m/3.96, m	29.3/ 29.4	1.85 m, 1.26 m
	CH[b]		1.30, m		1.24, m		
27/27′	CH	71.4	4.02, m	71.4	3.98, m	71.5	3.98, m
28/28′	CH_2	34.8	1.82, m	34.8/34.9	1.81, m	34.8 /38.9	1.80, m
			1.60, m		1.58, m		1.58, m
29/29′	CH	73.2	3.53, m	73.2	3.53, m	73.2	3.51, m
29/29′-OMe	CH_3	55.2	3.33, s	55.2	3.33, s	55.2	3.31, s
30/30′	CH_2	38.8	1.96, m	38.6/42.8	1.98, m/1.93, m	38.7	1.94, m
			1.18, m		1.16, m/1.16, m		1.19, m
31/31′	CH	64.5	3.69, m	64.5/64.4	3.68, m	64.5	3.68, m
31/31′-Me	CH_3	21.7	1.20, d (6.0)	21.7/21.8	1.20, brd/1.19, brd	21.7	1.17, brd/1.16, brd

[a] Data from COSY, HMQC, and HMBC experiments. [b] Data from DEPT for compound **2**. [c] No protons or carbons at these positions.

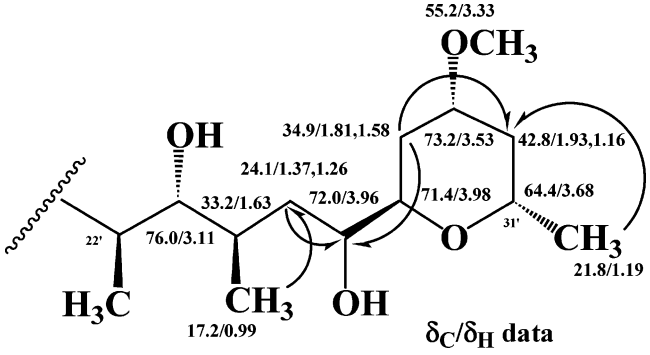

Figure 1. Key NMR data and HMBC correlations in partial structure of swinholide I (**2**).

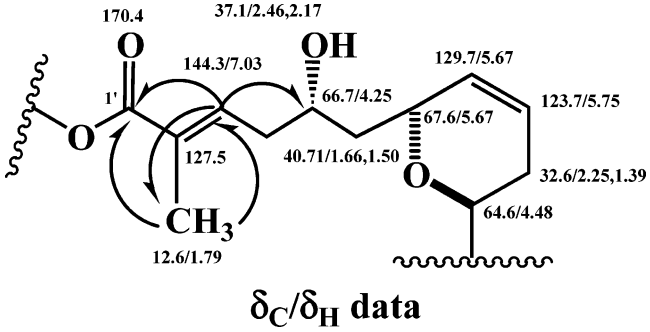

Figure 2. Key NMR data and HMBC correlations in partial structure of hurghadolide A (**3**).

The high-resolution positive FABMS of compound **3** showed that the molecular formula ($C_{76}H_{130}O_{20}$) was 26 mass units lower than that of swinholide A (**1**), indicating the loss of C_2H_2. The molecular formula of **3** requires 12 degrees of unsaturation, one less than that of swinholide A, suggesting the loss of one of the olefinic moieties in **3**. The ^{13}C NMR spectrum of swinholide A (**1**) shows six signals in the region between 153.2 and 113.2 ppm, corresponding to six pairs of equivalent carbons of C-2/2′ (δ 113.2, CH), C-3/3′ (δ 153.2, CH), C-4/4′ (δ 134.2, qC), C-5/5′ (δ 142.2, CH), C-10/10′ (δ 129.8, CH), and C-11/11′ (δ 123.2, CH), together with the lactone signal of C-1/1′ at δ 170.0 (Table 1). In comparison to **1**, the downfield region of the ^{13}C NMR spectrum of **3** showed 10 resonances for olefinic carbons in the region 153.2−113.5 ppm instead of six signals, together with two resonances at δ 170.3 and 170.4 for the lactone carbons C-1 and C-1′, respectively. The presence of 10 signals (eight methines and two quaternary carbons) in the olefinic region of **3** instead of six signals in the same region

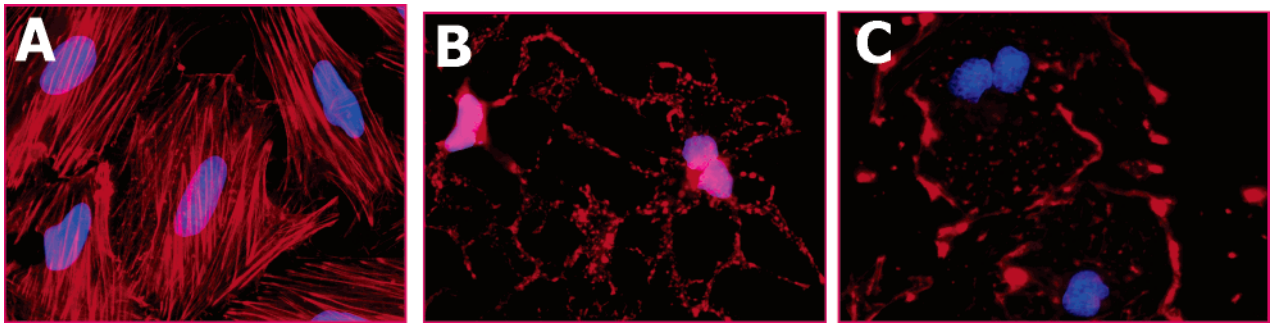

Figure 3. Effect of swinholide I (**2**) and hurghadolide A (**3**) on the actin cytoskeleton of A-10 cells. The compounds were added, and after 24 h, cells were processed and exposed to the microfilament-staining reagent TRITC-phalloidin (visualized as red) and to the DNA-reactive compound DAPI (visualized as blue). The control was treated with vehicle. (A) Control cells. (B) Treatment of the cells with swinholide I at 70 nM, which caused complete loss of the cellular microfilament network and generated binucleated cells. (C) Treatment of the cells with hurghadolide A at 7.3 nM, which caused complete loss of the cellular microfilament network and generated binucleated cells.

of **1** suggested the loss of symmetry in the dilactone skeleton of **3**, most likely through the absence of one double-bond moiety in half of the molecule (Table 1). Furthermore, the ^{1}H NMR spectrum of **3** showed resonances for eight nonequivalent protons in the region 7.60−5.64 ppm, instead of resonances for five pairs of equivalent protons (H-2/2′, H-3/3′, H-5/5′, H10/10′, H-11/11′) between 7.58 and 5.69 ppm in **1** (Table 1). The assignment of the partial fragments of the dilactone skeleton as well as the assignment of the ^{1}H and ^{13}C NMR resonances in **3** were supported by extensive study of ^{1}H, ^{13}C NMR, ^{1}H,^{1}H-COSY, HMQC, and HMBC spectra (Table 1 and Figure 2). The loss of the C-2′/C-3′ fragment at one side of the molecule caused twinning of most of the ^{1}H and ^{13}C NMR signals in the molecule (Table 1). The absence of the C-2′/C-3′ olefin in **3** was unambiguously supported from HMBC cross-peaks of H-3′/C-1′, Me-2′/C-1′, Me-2′/C-3′, H-3′/Me-2′, and H-3′/C-5′ (Figure 2).[8]

The relative stereochemistries of swinholide I (**2**) and hurghadolide A (**3**) are proposed on the basis of the similarity of the J_{HH} values between **2** and **3** and swinholide A (**1**). The existence of hurghadolide A with its unprecedented unsymmetrical 42-membered dilactone skeleton in *T. swinhoei* is noteworthy from the viewpoint of the biosynthesis of such metabolites and the chemotaxonomy of the Lithistid sponges.

Actin-Microfilament Disruption Assay.[9] Swinholide-type macrolides display their cytotoxicity by disruption of the actin cytoskeleton.[10] One dimeric molecule binds simultaneously to two molecules of G-actin, forming a tertiary complex with the side chain of the macrolide (C-21/C-21′ to C-27/C-27′), thus inhibiting polymerization by sequestrating G-actin.[11] In addition, swinholides cause breakage of filamentous actin strands.[12] To evaluate the influence of the absence of the C-2′/C-3′ moiety, the shortage of the ring skeleton, and the loss of the symmetry in hurghadolide A (**3**) as well as the introduction of an OH moiety at C-26′ in swinholide I (**2**), the microfilament-disrupting effects of both compounds were evaluated in A-10 cells using rhodamine phalloidin as previously described.[8] Briefly, cells were treated with the compounds for 24 h and fixed. Microfilaments were visualized with rhodamine-phalloidin and nuclei visualized with DAPI. Hurghadolide A (**3**) was a potent disruptor of cellular microfilaments. At a concentration of 7.3 nM most of the microfilaments were lost and cells with double nuclei were observed (Figure 3C). Normal actin dynamics are necessary for the formation of the contractile ring that separates the two daughter cells in cell division. Interruption of actin dynamics does not inhibit mitosis, so two normal nuclei are formed, but it does inhibit cytokinesis leading to double nucleated cells. The effects of hurghadolide A are reminiscent of the effects of the swinholide A derivative, ankaraholide A.[6b] The ability of swinholide I (**2**) to disrupt microfilaments was also evaluated. The results show that it is slightly less potent than hurghadolide A, with total loss of microfilaments occurring at 70.0 nM (Figure 3B). It also caused the appearance of cells with double nuclei, suggesting that cytokinesis was inhibited. Phenotypically there were slight differences between the effects of hurghadolide A and swinholide I in A-10 cells (Figure 3). Although both caused total loss of cellular microfilaments, cells treated with hurghadolide A maintained a relatively normal cell shape. Cells treated with swinholide I collapsed and formed neuron-like structures at the concentration that caused total microfilament loss.

In conclusion, swinholide I showed potent cytotoxicity against the human colon carcinoma cell line (HCT-116) with an IC_{50} of 5.6 nM, while the IC_{50} for hurghadolide A was 365 nM. In contrast, in the actin-microfilament-disrupting assay hurghadolide A was 10 times more potent than swinholide A at disrupting microfilaments. These data highlight some interesting mechanistic differences between these two compounds. The data suggest that swinholide I is more selective for cancer cells and might have additional mechanisms of initiating cytotoxicity in cancer cells as compared to the embryonic smooth muscle cells that are used in the microfilament-disrupting assay. Further mechanistic assays should be conducted with these compounds to identify the nature of their differences for cancer cells and for actin-disrupting activity.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO DIP-370 digital polarimeter using $CHCl_3$ or MeOH at 25 °C at the sodium D line (589 nm). UV spectra were recorded on a Hitachi 300 spectrometer. NMR spectra were determined on Varian Unity INOVA 500 and 600 instruments (500/600 MHz for ^{1}H and 125/150 MHz for ^{13}C NMR). NMR chemical shifts were referenced to $CDCl_3$ solvent signals (δ_H 7.24; δ_C 77.0 ppm). Homonuclear ^{1}H connectivities were determined by using the 2D double-quantum-filtered COSY. One-bond heteronuclear ^{1}H−^{13}C connectivities were determined by a 2D proton-detected HMQC experiment. Two- and three-bond ^{1}H−^{13}C connectivities were determined by a 2D proton-detected HMBC experiment. Positive HRFABMS spectra were determined on a Finnigan MAT-312 using 3-NBA/NaCl. HPLC purification was performed on a preparative C_{18} HPLC column (Cosmosil ARII, 250 × 20 mm, 5 μm, Waters).

Biological Materials. The sponge is cylindrical in shape and dark red-brown in color. The cutoff fragment measures 7.5 cm high and 4.5 cm in diameter. It has a central canal of 1.5 cm diameter leading to a narrow vent with a sphincter-like membrane at the top. The in-situ photo shows the vent to be similar in diameter to the central canal. The surface is slightly bumpy, generally smooth, but furrowed lengthwise. The ectosomal skeleton consists of a dense mass of curved acanthomicrorhabds of 15−24 × 2−3 μm, overlying a loose reticulation of reduced phyllotriaenes with cladome spanning 120−180 μm and thin undivided cladi 55−120 × 4−7 μm in size. A subectosomal region measuring about 1 mm in thickness bridges an area devoid of desmas, the skeleton of which consists of bundles of strongylotes, measuring 25−70 μm in diameter, enclosing 4−20 strongylotes. The latter are

Table 2. Cytotoxic and Antifungal Activities for Compounds **2** and **3**[a]

	HCT-116	*C. albicans* (W.T.)[d]	*C. albicans* (AmBR)[e]
compound	IC_{50} (μg/mL)	MIC (μg/mL)	MIC (μg/mL)
swinholide I (**2**)	0.008	62.2	500
hurghadolide A (**3**)	0.500	31.3	31.3
etoposide[b]	1.200		
amphotericin B[c]		1.56	

[a] Upper limit on the antifungal assay is 500 μg/mL. [b] Positive cytotoxicity control. [c] Positive antifungal control. [d] Wild-type. [e] Amphotericin B-resistant type.

slightly anisotylote with either end more or less swollen, 405−620 × 3−6 μm in size. The choanosomal skeleton consists of a loose reticulation of tetraclone desmas strengthened by bundles of strongylotes. Desmas cladomes measure 400−550 μm, rhabds smooth, 120−230 × 15−20 μm, and cladi smooth with simple zygoses, 150−250 × 12−16 μm. Compared with the type specimen there are some differences (lighter skeletal, smooth instead of tuberculated desmas, shorter strongylotes), which are judged to be infraspecific variation. The voucher fragment is registered in the collection of the Zoological Museum of Amsterdam under registration number POR 16637 and in the Red Sea Invertebrates Collection at Faculty of Pharmacy, Suez Canal University, under registration number DY-RS-59.

Purification of Compounds 1−3. The frozen sponge materials (3.15 kg, wet wt) were extracted three times (3 × 1500 mL) with a mixture of MeOH/CH_2Cl_2 (1:1) at room temperature. The combined organic extracts were concentrated under reduced pressure and suspended in 1000 mL of MeOH/H_2O (9:1). The resulting mixture was extracted with *n*-hexane (3 × 400 mL) to give 8.2 g of *n*-hexane residue. The remaining methanolic layer was diluted with H_2O to (3:2) MeOH/H_2O and then extracted with CH_2Cl_2 (3 × 400 mL) to give 3.1 g of CH_2Cl_2 residue. The cytotoxic CH_2Cl_2 residue was dissolved in MeOH and subjected to size exclusion chromatography on a Sephadex LH-20 column equilibrated with MeOH to give nine major fractions. Fraction 4 (730 mg) was subjected to ODS flash chromatography using 30% aqueous MeOH through pure MeOH to afford 10 fractions. The potent cytotoxic swinholides-rich fraction (fraction 9), which eluted with MeOH (136 mg), was purified on a preparative C_{18} HPLC column using 50% MeCN at a flow rate of 6 mL/min to give compounds **1** (80.5 mg), **2** (5.7 mg), and **3** (12.5 mg).

Compounds **2** and **3** were evaluated for their antifungal activity against two strains of *Candida albicans* (wild-type and amphotericin-resistant type). The results are shown in Table 2. Human colon adenocarcinoma (HCT-116) cells were incubated overnight at 37 °C in 5% CO_2/air in microtiter plates.[13] Test materials, etoposide (positive control), and DMSO (negative control) were added to the top row of a 96-well microtiter plate and serially diluted (1:4) downward. After a 72 h incubation, cell viability was determined colorimetrically using a Molecular Devices Emax microplate reader (490 nm), recording the amount of MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium) reduced to formazan using the CellTiter 96 AQueous nonradioactive cell proliferation protocol (Promega). Minimum inhibitory concentration ($IC_{50,}$ μg/mL) values were calculated using the program SOFTmax PRO (Molecular Devices). The results of the cytotoxicity are shown in Table 2.

Swinholide A (1): light yellow solid; $[\alpha]^{25}_D$ +16.5 (*c* 0.1, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 275 nm (5.03); NMR data, see Table 1; positive HRFABMS *m*/*z* 1411.9209 (calcd for $C_{78}H_{132}NaO_{20}$ $[M + Na]^+$, 1411.9210).

Swinholide I (2): light yellow solid; $[\alpha]^{25}_D$ −42.5 (*c* 0.045, MeOH); UV (MeOH) λ_{max} (log ϵ) 274 nm (4.58); NMR data, see Table 1; positive HRFABMS *m*/*z* 1427.9158 (calcd for $C_{78}H_{132}NaO_{21}$ $[M + Na]^+$, 1427.9159).

Hurghadolide A (3): light yellow solid; $[\alpha]^{25}_D$ −29.4 (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ϵ) 274 nm (4.95); NMR data, see Table 1; positive HRFABMS *m*/*z* 1385.9059 (calcd for $C_{76}H_{130}NaO_{20}$, $[M + Na]^+$, 1385.9053).

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **1**−**3** as well as underwater photograph of the sponge *Theonella swinhoei*. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep*. **2005**, *22*, 15−61, and the previous reviews in this series.
(2) Kashman, Y.; Carmely, S. *Tetrahedron Lett.* **1985**, *26*, 511−514.
(3) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *22*, 2963−2966.
(4) (a) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Yamashita, M.; Kitagawa, I. *Chem. Pharm. Bull*. **1990**, *38*, 2409−2418. (b) Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M.; Tanaka, J.; Doi, M.; Ishida, T. *J. Am. Chem. Soc.* **1990**, *112*, 3710−3712. (c) Doi, M.; Ishida, T.; Kobayashi, M.; Kitagawa, I. *J. Org. Chem.* **1991**, *56*, 3629−3632.
(5) (a) Kobayashi, M.; Tanaka, J.; Katori, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2960−2966. (b) Tsukamoto, S.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3185−3188. (c) Dumdei, E. J.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Org. Chem.* **1997**, *62*, 2635−2639. (d) Sakai, R.; Higa, T.; Kashman, Y. *Chem. Lett.* **1986**, 1499−1502. (e) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Sakai, R.; Higa, T.; Kashman, Y. *Tetrahedron Lett.* **1987**, *28*, 6225−6228. (f) Tanaka, J.; Higa, T.; Motomasa, K.; Kitagawa, I. *Chem. Pharm. Bull*. **1990**, *38*, 2967−2970. (g) Todd, J. S.; Alvi, K. A.; Crews, P. *Tetrahedron Lett*. **1992**, *33*, 441−442.
(6) (a) Bewley, C. A.; Holland, N. D.; Faulkner, D. J. *Experientia* **1996**, *52*, 716−722. (b) Andrianasolo, E. H.; Gross, H.; Goeger, D.; Musafija-Girt, M.; McPhail, K.; Leal, R. M.; Mooberry, S. L.; Gerwick, W. H. *Org. Lett*. **2005**, *7*, 1375−1378.
(7) (a) Youssef, D. T. A.; Shaala, L. A.; Emara. S. *J. Nat. Prod*. **2005**, *68*, 1782−1784. (b) Youssef, D. T. A. *J. Nat. Prod*. **2005**, *68*, 1416−1419. (c) Youssef, D. T. A. *J. Nat. Prod*. **2004**, *67*, 112−114. (d) Youssef, D. T. A.; van Soest, R. W. M.; Fusetani, N. *J. Nat. Prod*. **2003**, *66*, 861−862. (e) Youssef, D. T. A.; van Soest, R. W. M.; Fusetani, N. *J. Nat. Prod*. **2003**, *66*, 679−681. (f) Youssef, D. T. A.; Yamaki, R. K.; Kelly, M.; Scheuer, P. J. *J. Nat. Prod.* **2002**, *65*, 2−6. (g) Youssef, D. T. A.; Yoshida, W. Y.; Kelly, M.; Scheuer, P. J. *J. Nat. Prod*. **2001**, *64*, 1332−1335. (h) Youssef, D. T. A.; Yoshida, W. Y.; Kelly, M.; Scheuer, P. J. *J. Nat. Prod*. **2000**, *63*, 1406−1410.
(8) The numbering 1′, 2′, 3′, 4′, and 5′ in hurghadolide A (**3**) corresponds to 1′, 4′, 5′, 6′, and 7′ in swinholide A (**1**), respectively.
(9) Harrigan, G. G.; Yoshida, W.; Moore, R. E. Nagle, D. G.; Park, P. U.; Biggs, J.; Paul, V. J.; Mooberry, S. L.; Corbett, T. H.; Valeriote, F. A. *J. Nat. Prod*. **1998**, *61*, 1221−1225.
(10) Bubb, M. R.; Spector, I.; Bershadsky, A. D.; Korn, E. D. *J. Biol. Chem.* **1995**, *270*, 3463−3466.
(11) Saito, S.; Watabe, S.; Ozaki, H.; Kobayashi, M.; Suzuki, T.; Kobayashi, H.; Fusetani, N.; Karaki, H. *J. Biochem*. **1998**, *123*, 571−578.
(12) Terry, D. R.; Spector, I.; Higa, T.; Bubb, M. R. *J. Biol. Chem.* **1997**, *272*, 7841−7845.
(13) Soria-Mercado, I. E.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. *J. Nat. Prod*. **2005**, *68*, 904−910.

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