Journal of Natural Products
Vol. 58, No. 7, pp. 1120-1125, July 1995

MYCALOLIDES D AND E, NEW CYTOTOXIC MACROLIDES FROM A COLLECTION OF THE STONY CORAL *TUBASTREA FAULKNERI*

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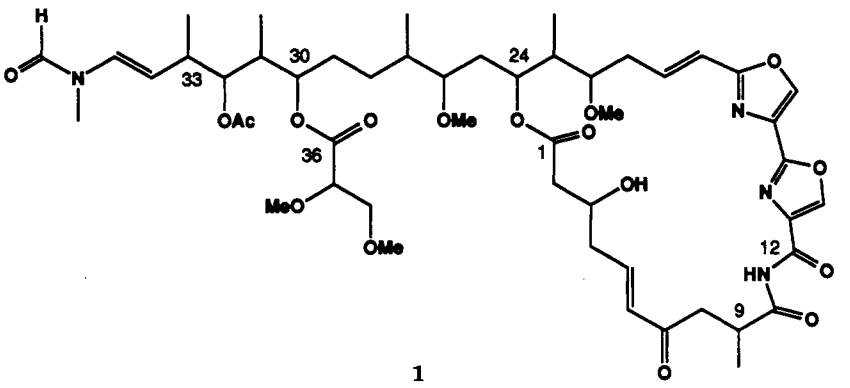
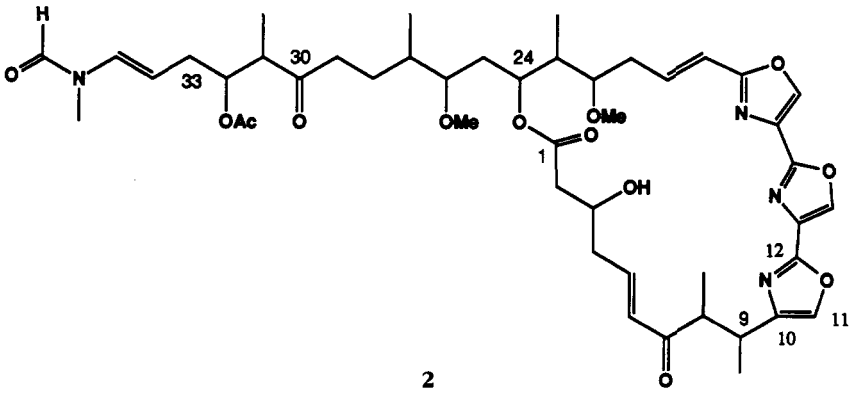
ABSTRACT.—Fractionation of a cytotoxic extract of the stony coral *Tubastrea faulkneri* yielded a series of cytotoxic polyoxazole macrolides and several noncytotoxic indole derivatives. Two new macrolides, mycalolides D [**1**] and E [**2**], were isolated and identified, in addition to the known compound mycalolide C [**3**]. The macrolide structures were elucidated by detailed analysis of their spectroscopic data and by comparison with related compounds.

Stony (scleractinian) corals in the genus *Tubastrea* (Dendrophylliidae) have been reported to be a source of biologically active alkaloids (1,2), including aplysinopsin (3) and related brominated indole derivatives (4,5). They have not previously been known to contain macrolide metabolites. An extract from an Australian collection of *Tubastrea faulkneri* Wells was found to be cytotoxic in the 60-cell-line antitumor screen of the NCI (6,7). Bioassay-directed fractionation of the extract provided an inactive fraction which contained aplysinopsin-type alkaloids and a cytotoxic fraction rich in polyoxazole macrolides. Described herein is the isolation, structure elucidation, and cytotoxicity profile of two new macrolides, mycalolides D [**1**] and E [**2**], along with the known mycalolide C [**3**], from this collection of *Tubastrea faulkneri*.

An organic extract (2.2 g) of *T. faulkneri*, from the Great Barrier Reef of Australia, was subjected to a solvent-solvent partitioning protocol (8) that concentrated the cytotoxic activity into CCl_4- and $CHCl_3$-soluble fractions. The CCl_4-soluble fraction was further separated by gel permeation cc on Sephadex LH-20 and diol bonded-phase hplc to give mycalolides C [**3**] (14 mg) and D [**1**] (6 mg). The $CHCl_3$ partition fraction was chromatographed on diol packing by vlc. Several of the early-eluting vlc fractions were subjected to diol hplc to give indole-3-carboxaldehyde (1 mg) (9,10), 6-bromoindole-3-carboxaldehyde (2 mg) (10,11), and a mixture of macrolides. Purification of this macrolide mixture by C_{18} hplc gave mycalolide E [**2**] (1 mg) and an additional 5 mg of **3**. The very late eluting material from the diol vlc column was subjected to C_{18} hplc to afford the



1



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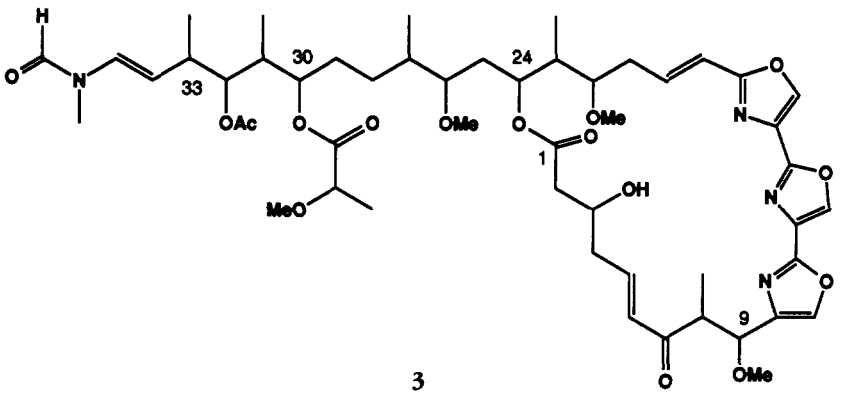
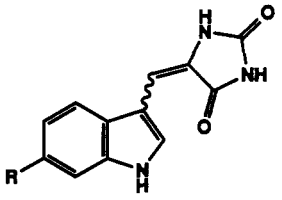


3

yellow pigment 3′-deamino-2′,4′-*bis*(demethyl)-3′-oxoaplysinopsin [**4**] (3 mg) (4) as a 4:1 mixture of *Z*/*E* geometrical isomers and a similar 4:1 *Z*/*E* isomeric mixture of the 6-bromo analogue [**5**] (3 mg) (4). All of the indole derivatives were identified by comparison of their physical and spectral characteristics with those described in the literature.

The molecular formula of compound **3**, obtained as a colorless gum, was established by high-resolution fabms as $C_{51}H_{72}N_4O_{16}$. The ^{1}H- and ^{13}C-nmr data that we recorded were virtually identical to spectral data reported for mycalolide C [**3**], isolated previously from a sponge (12).



4 R=H
5 R=Br

The molecular formula of mycalolide D [**1**] was established as $C_{50}H_{72}N_4O_{17}$ by fabms and had uv (λ max 228 and 260 nm) and ir (ν max 3380, 1748, 1734, 1700, 1652 cm^{-1}) absorptions appropriate for an oxazole-containing macrolide. The ^{1}H- and ^{13}C-nmr spectra of **1** (Table 1) showed close correspondence to those reported for mycalolide C [**3**]. Restricted rotation around the C-N bond of the *N*-methyl formamide resulted in doubled ^{1}H- and ^{13}C-nmr signals, in a ratio of approximately 2:1, for those groups close to the unsaturated formamide moiety. This spectral feature, previously observed for the mycalolides (12), ulapualides (13), kabiramides (14,15), halichondramides (16,17), and jaspisamides (18), is characteristic of this class of macrolide. The 14

TABLE 1. Nmr Data ($CDCl_3$) for Mycalolides D [**1**] and E [**2**].

Carbon	Mycalolide D [**1**][a,b]				Mycalolide E [**2**][a]
	$\delta^{13}C$		$\delta^{1}H$[c]	HMBC Correlations	$\delta^{1}H$[c]
1	171.7				
2	41.6		2.45 m		2.46 m
			2.48 m		2.54 m
3	67.1		4.27 m	C-1, C-2, C-5	4.38 m
4	39.3		2.39 m		2.40 m
			2.42 m		2.52 m
5	144.4		7.08 dt, 15.6, 7.3	C-3, C-4, C-7	7.18 dd, 16.1, 7.2
6	131.1		6.26 br d, 15.6	C-4, C-7	6.08 br d, 16.1
7	198.2				
8	45.1		2.67 m	C-7, C-9, C-9-Me, C-10	2.54 m
			2.71 m		
Me-8					1.03 (3H) d, 6.8
9	37.6		3.05 m	C-7, C-9-Me, C-10	3.37 m
Me-9	16.2		1.23 (3H) d, 6.8	C-8, C-9, C-10	1.31 (3H) d, 6.8
10	173.5				
11					7.42 s
12	157.8				
13	136.6				
14	143.2		8.33 s	C-13, C-15	8.04 s
15	155.3				
16	130.1				
17	138.6		8.10 s	C-16, C-19	8.03 s
18	162.7				
19	117.5		6.42 dd, 16.1, 3.5	C-18, C-20	6.35 br d, 15.6
20	139.2		6.95 dt, 16.1, 7.3	C-18, C-22	7.06 m
21	33.4		2.44 m		2.42 m
			2.67 m		2.65 m
22	79.4		3.29 m		3.62 m
OMe-22	57.7		3.32 (3H) s	C-22	3.32 (3H) s
23	39.9		1.72 m		1.92 m
Me-23	9.4		0.85 (3H) d, 7.3	C-22, C-23, C-24	0.94 (3H) d, 6.8
24	73.0		5.23 m	C-1, C-25	5.22 m
25	32.1		1.42 m		1.55 m
			1.54 m		1.60 m
26	81.6	[81.5]	2.91 m	C-26-OMe, C-27-Me, C-28	2.96 m
OMe-26	57.8	[57.7]	3.27 (3H) s	C-26	3.28 s
27	34.6	[34.5]	1.72 m		1.60 m
Me-27	15.6		0.81 (3H) d, 6.8	C-26, C-27, C-28	0.82 (3H) d, 6.8
28	27.0		1.42 (2H) m		1.24 m
					1.80 m
29	30.5	[30.1]	1.54 (2H) m		2.48 (2H) m
30	73.1	[73.2]	5.09 m	C-31, C-31-Me, C-32, C-36	
31	37.6		1.80 m		2.75 m
Me-31	9.8		0.99 (3H) d, 6.8		1.06 (3H) d, 6.8
32	76.4		4.75 m	C-32-OAc, C-34	5.12 dd, 8.8, 4.1
OAc-32	170.6	[170.4]			
	21.0		2.06 (3H) s		1.99 (3H) s
33	37.0	[37.1]	2.50 m		2.46 (2H) m
Me-33	19.4	[19.5]	0.95 (3H) d, 6.8	C-32, C-33, C-34	
34	110.3	[112.1]	4.94 [4.96] dd, 14.1, 9.3	C-32, C-33-Me, C-35	4.95 [4.98] dd, 14.2, 9.1
35	129.4	[125.4]	6.48 [7.13] d, 14.1	C-33, C-35-NMe, C-35-NCHO	6.48 [7.12] d, 14.2
NMe-35	27.6	[33.4]	2.99 [3.03] (3H) s	C-35, C-35-NCHO	3.01 [3.05] (3H) s
NCHO-35	162.1	[160.9]	8.27 [8.05] s	C-35, C-35-NMe	8.27 [8.06] s
36	170.4				
37	80.7		3.90 m	C-36, C-37-OMe, C-38	
OMe-37	58.7		3.46 (3H) s	C-37	
38	73.1		3.60 m	C-36, C-38-OMe	
			3.62 m		
OMe-38	59.4		3.37 (3H) s	C-38	
NH			10.19 br s	C-10, C-12	

[a]Values in square brackets are for the minor (*Z*) double bond isomer.
[b]For convenience of comparison, C-11 in **1** was omitted intentionally, as was done with a halichondramide imide (16).
[c]δ, multiplicity, *J* (Hz).

Hz coupling between H-34[1] and H-35, and nOe interactions between the formamide *N*-methyl protons (δ 2.99) and the H-34 olefinic proton (δ 4.94), established that the $\Delta^{34,35}$ bond had *E* (trans) geometry. The C-5–C-6 and C-19–C-20 double bonds could be assigned as *E* based on the large vicinal couplings (J=15.6 and 16.1 Hz, respectively) observed between the olefinic protons. The substitution of methoxy groups at C-22 and C-26 and an acetate at C-32 was confirmed by HMBC correlations. The principal differences between the spectra of **1** and **3** were variations in the C-30 acyl groups and in the C-8–C-12 region. Although compound **3** is characterized by a 2-*O*-methyllactate group at C-30, compound **1** showed ^{1}H- [methyl singlets at δ 3.37 and 3.46; 1H multiplets at δ 3.60, 3.62, and 3.90] and ^{13}C-nmr [δ 170.4, 80.7, 73.1, 59.4, 58.7] resonances appropriate for a 2,3-di-*O*-methylglycerate substituent. COSY correlations supported this assignment and an HMBC correlation from the C-30 methine proton (δ 5.09) to C-36 (δ 170.4) confirmed its substitution at C-30. Compound **1** revealed two ^{1}H-nmr singlets (δ 8.10, 8.33) and six ^{13}C-nmr signals (δ 130.1, 136.6, 138.6, 143.2, 155.3, 162.7) indicative of two adjacent disubstituted oxazoles. HMBC correlations required that one oxazole was conjugated to C-19, while the proton (δ 8.33) of the second oxazole showed a three-bond correlation to the adjacent C-12 (δ 157.8) imide carbonyl group. The imide NH (δ 10.19) correlated with both the C-10 (δ 173.5) and C-12 imide carbonyls, while correlations from the C-9 methine proton (δ 3.05) and one of the C-8 methylene protons (δ 2.67) to C-10 confirmed the placement of the imide group. The presence of three contiguous oxazole rings is typical of this class of macrolide; however, replacement of the C-10–C-12 oxazole with an imide in mycalolide D [**1**] is reminiscent of a *Halichondria* macrolide, which had an imide in place of the C-16–C-18 oxazole (16). Substitution of a methyl group at C-9, similar to the ulapualides (13), was confirmed by an HMBC correlation from the methyl protons to C-10. Thus, we were able to assign structure **1** to mycalolide D.

Mycalolide E [**2**], isolated as a minor constituent, displayed uv, ir, and ^{1}H-nmr spectra similar to those of mycalolide C [**3**]. The hrfabms revealed a MH^+ pseudomolecular ion at *m/z* 879.4434, which established the molecular formula as $C_{46}H_{62}N_5O_{13}$. The structure of **2** was deduced primarily from ^{1}H-nmr studies and comparison of its spectral data with those of **3** and other related compounds in the literature. By COSY analysis and spectral comparison, the C-1 through C-8 portion of **2** was shown to be identical to that of **3**. However, the C-9 methoxy substituent of **3** was replaced by a methyl group (δ 1.31) in **2**. Irradiation of the C-9 methyl signal induced strong nOe interactions with the C-8 methyl and H-11. Mycalolide E [**2**] is the first compound in this class to have methyl substituents at both C-8 and C-9. Three singlet aromatic resonances characteristic of a trisoxazole constellation were observed in **2**. Again, the C-19–C-29 portion of **2** was shown by direct spectral comparison and COSY and nOe results to be identical to the corresponding regions in compounds **1** and **3**. The lack of an acyl group and methine proton at C-30, coupled with deshielded signals for the C-29 methylene protons (δ 2.48, 2H, m) and the C-31 methine proton (δ 2.75, m) indicated a ketone at C-30. A C-30 ketone has been observed in a majority of the trisoxazole macrolides (12–18). Comparative analysis indicated that C-31 through the terminal *N*-methyl formamide group of **2** was clearly related to that section of compounds **1** and **3**,

[1]For convenience of comparison, C-11 in **1** was intentionally omitted in the numbering scheme, as has been done for the imide derivative of halichondramide (16).

with the exception of C-33. In **2**, C-33 is an allylic methylene, while C-33 in both **1** and **3** is substituted with a methyl group. The C-33 protons (δ 2.46, 2H, m) showed nOe interactions with H-35 and vicinal couplings to the C-32 methine proton and the C-34 olefinic proton. The spectral data we recorded for compound **2** were in good agreement with data reported for C-33-demethylhalichondramides (16) and jaspisamides (18). While the structure of mycalolide E [**2**] has been deduced by spectral analyses, confirmation using heteronuclear correlation experiments was not possible due to the limited supply of the compound.

Mycalolides C [**3**] and D [**1**] were screened against the NCI's 60-human-tumor cell line panel. They showed modest general cytotoxicity with average LC_{50} values of 2.5 μM and 0.6 μM, respectively. They did not produce a pattern or a degree of differential cytotoxicity of sufficient interest to encourage any further study. Mycalolide E [**2**] was not tested due to insufficient material.

Prior to this investigation, macrocyclic lactones containing two or three contiguous oxazole rings have only been isolated from nudibranchs and their egg masses (13–16), and from sponges of the genera *Halichondria* (16,17), *Jaspis* (18), and *Mycale* (12). Therefore, it was surprising to find this class of compound in a coelenterate extract. Examination of photographs of the original *T. faulkneri* collection and voucher specimens did not reveal any obvious nudibranch or sponge tissue. Thus, it appears the distribution of polyoxazole macrolides can be expanded to include corals in the genus *Tubastrea*.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Instrumentation and standard procedures have been described elsewhere (19,20).

ANIMAL MATERIAL.—Samples of *Tubastrea faulkneri* Wells were collected along Salamander Reef at Cape Cleveland, the Great Barrier Reef, northeast Australia, by Dr. Peter Murphy and colleagues of the Australian Institute of Marine Science (AIMS). Voucher specimens (Q66C1269) from this collection are maintained at the Queensland Museum in Brisbane.

EXTRACTION AND ISOLATION.—Fresh samples were frozen after collection and stored at −20° until they were processed. Frozen samples (614 g) were mixed with dry ice, ground to a coarse powder, and then extracted with H_2O. The marc was refrozen, lyophilized, and sequentially extracted with MeOH-CH_2Cl_2 (1:1) and 100% MeOH. The combined organic extracts were evaporated at reduced pressure to give 2.84 g of a brown tar.

The total extract was separated by a liquid-liquid partitioning protocol (8) which concentrated the antitumor activity into CCl_4 and $CHCl_3$ fractions. The CCl_4-soluble material (247 mg) was fractionated by gel permeation cc on Sephadex LH-20 eluting with hexane-CH_2Cl_2-MeOH (2:5:1). An early eluting LH-20 fraction (130 mg) retained the antitumor activity. This fraction was further purified by hplc on a wide-pore diol bonded-phase column (YMC, 1×20 cm, 300 Å) with hexane-CH_2Cl_2-MeOH (15:49:1) to give mycalolides C [**3**] (14 mg) and D [**1**] (6 mg). The $CHCl_3$-soluble fraction from the initial liquid partitioning step was subjected to diol (YMC) vlc with a step-gradient elution. The cytotoxic material eluted with 100% CH_2Cl_2 through CH_2Cl_2-MeOH (97:3) was separated by diol hplc with hexane-CH_2Cl_2-MeOH (15:49:1) to yield indole-3-carboxaldehyde (1 mg), 6-bromoindole-3-carboxaldehyde (2 mg), and a mixture of macrolides that were ultimately purified by C_{18} hplc (1×25 cm column), using MeOH-H_2O (4:1) to afford mycalolide E [**2**] (1 mg) and an additional 5 mg of **3**. Similar C_{18} hplc purification of the vlc fraction that eluted with MeOH-H_2O (3:1) afforded 3′-deamino-2′,4′-*bis*(demethyl)-3′-oxoaplysinopsin [**4**] (3 mg) as a 4:1 *Z*/*E* mixture of double bond isomers and the corresponding 6-bromo analogues [**5**] (3 mg) as a similar 4:1 *Z*/*E* mixture.

Mycalolide D [**1**].—Colorless gum; $[\alpha]_D$ −19.5° (*c*=0.5, $CHCl_3$); positive-ion hrfabms *m/z* 1001.4980 (MH^+, $C_{50}H_{73}N_4O_{17}$, calcd 1001.4970) and negative-ion fabms *m/z* 999 ($[M-H]^-$, appropriate for $C_{50}H_{71}N_4O_{17}$); uv (MeOH) λ max 228 (log ε 4.68), 260 sh (4.47) nm; ir (film) ν max 3380, 1748, 1734, 1700, 1652, 1576, 1558, 1540, 1506, 1456, 1236, 1108 cm^{-1}; ^1H- and ^{13}C-nmr data, see Table 1.

Mycalolide E [**2**].—Colorless gum; $[\alpha]_D$ −39.0° (*c*=0.1, $CHCl_3$); positive-ion hrfabms *m/z* 879.4434 (MH^+, $C_{46}H_{63}N_4O_{13}$, calcd 879.4391); uv (MeOH) λ max 231 (log ε 4.52), 254 (4.49) nm; ir (film) ν max 3370, 1729, 1658, 1462, 1370, 1234, 1092, 917 cm^{-1}; ^1H-nmr data, see Table 1.

ANTITUMOR ASSAY AND SCREENING DATA SUM-

MARY.—DMSO solutions of compounds **1** and **3** were assayed in the NCI's in vitro disease oriented antitumor screening panel (6). Data reporting format and response parameter definitions are published elsewhere (7). The negative $\log_{10}$ (M) GI_{50}, TGI, and LC_{50} values, respectively, are listed below for compound **1** by tumor type, with the individual cell line identifiers. Leukemia: CCRF-CEM (7.64, 6.82, >6.00), HL-60 (TB) (7.57, 7.18, 6.66), K-562 (7.82, 6.82, 6.08), MOLT-4 (7.24, 6.92, >6.00), RPMI-8226 (7.60, 6.96, >6.00), SR (7.38, 6.92, >6.00). Non-small cell lung: A549/ATCC (7.42, 6.68, >6.00), EKVX (7.03, 6.32, >6.00), HOP-62 (7.37, 6.92, 6.15), HOP-92 (7.51, 7.00, 6.11), NCI-H226 (7.36, 6.85, 6.35), NCI-H23 (6.96, 6.31, 6.01), NCI-H322M (6.89, 6.14, >6.00), NCI-H460 (7.60, 6.68, 6.28), NCI-H522 (7.46, 6.72, 6.02). Colon: COLO 205 (7.52, 6.89, 6.43), HCC-2998 (7.00, 6.36, 6.08), HCT-116 (7.14, 6.37, 6.03), HCT-15 (7.55, 6.62, 6.01), HT29 (7.70, 6.72, >6.00), KM12 (7.15, 6.43, >6.00), SW-620 (7.52, 6.28, >6.00). Brain: SF-268 (7.15, 6.48, >6.00), SF-295 (7.38, 6.96, 6.29), SF-539 (7.21, 6.62, 6.06), SNB-19 (6.92, 6.30, >6.00), SNB-75 (8.29, 7.60, 7.12), U251 (7.44, 7.05, 6.52). Melanoma: LOX IMVI (7.92, 7.54, 7.19), MALME-3M (7.80, 6.96, 6.12), M14 (7.48, 7.10, 6.36), SK-MEL-2 (7.68, 6.92, 6.12), SK-MEL-28 (7.62, 7.00, >6.00), SK-MEL-5 (7.28, 6.96, 6.68), UACC-257 (7.48, 7.10, 6.57), UACC-62 (7.39, 7.02, 6.36). Ovary: IGROV1 (7.48, 7.01, 6.37), OVCAR-3 (7.43, 7.12, 6.59), OVCAR-4 (7.82, 6.77, 6.18), OVCAR-5 (7.11, 6.57, 6.02), OVCAR-8 (7.30, 6.82, >6.00), SK-OV-3 (7.21, 6.70, 6.01). Kidney: 786-0 (7.44, 7.01, 6.30), A498 (7.40, 6.96, 6.39), ACHN (7.35, 6.36, >6.00), CAKI-1 (7.74, 7.34, 6.96), RXF-393 (7.35, 6.82, 6.05), SN12C (7.20, 6.15, >6.00), TK-10 (7.37, 7.01, 6.40), UO-31 (7.35, 6.96, 6.59). Prostate: PC-3 (7.49, 7.00, >6.00), DU-145 (6.96, 6.01, >6.00). Breast: MCF7 (7.14, 6.09, >6.00), MCF7/ADR-RES (7.07, 6.28, >6.00), MDA-MB-231/ATCC (7.42, 7.00, 6.54), HS 578T (7.48, 6.92, >6.00), MDA-MB-435 (7.46, 7.00, >6.00), MDA-N (7.36, 6.82, 6.01), BT-549 (7.47, 6.96, 6.48), T-47D (6.70, 6.35, >6.00).

ACKNOWLEDGMENTS

We thank P. Murphy (AIMS) for the collection of *Tubastrea faulkneri*, E.G.L. Koh for the taxonomic identification, L. Pannell, Laboratory of Analytical Chemistry, NIDDK, for mass spectral analyses, and A. Monks and D. Scudiero for the cytotoxicity screening.

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Received 18 January 1995