Table I. Association Energies (kcal/mol) of Monensin and Derivatives for Metal Ions in Methanol at 20 °C

compd	thallium(I)	sodium
1	−6.5 (±0.5), −6.0[5]	−8.1 (±0.8), −7.0[5], −8.5[6]
2a	−6.3 (±0.4)	−7.9 (±0.7)
2b	−4.6 (±0.2)	−6.3 (±0.5)
2c	−6.0 (±0.4)	−7.5 (±0.6)
2d	−5.3 (±0.3)	
1 methyl ester	−3.2 (±0.2)	

than any specific substituent or stereochemical array. The preorganization of the C2–C3 and C3–C4 bonds appears to contribute ~1 kcal/mol to binding (**1** or **2a** versus **2d**); however, conformational restraints which disfavor the native binding conformation can give larger reductions in binding energy (**1** or **2a** versus **2b**). It should also be noted that major modifications to the polyether structure can be made without elimination of ionophoric properties. These results are compatible with the view that the ion binding properties of the polyethers result from an accumulation of smaller effects which depend upon the properties of the component substructures. Finally, these molecules illustrate that the avoidance of +g/−g interactions can create an effective mechanism for an acyclic conformational lock and control the geometry of otherwise flexible structures.[7]

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(7) This work was supported by NIH Grant HL25634 and an SERC/NATO postdoctoral fellowship to P.W.S.

Patellazole C: A Novel Cytotoxic Macrolide from *Lissoclinum patella*

T. Mark Zabriskie,[†] Charles L. Mayne,[‡] and Chris M. Ireland*[,†,1]

Department of Medicinal Chemistry and Department of Chemistry University of Utah Salt Lake City, Utah 84112

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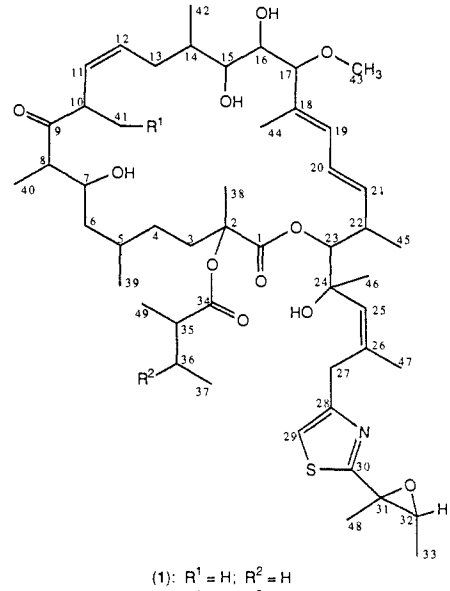
The didemnid tunicate *Lissoclinum patella* collected in Palau has previously been shown to produce a family of unique, cytotoxic cyclic peptides, all containing thiazole amino acids.[2] In contrast, we now report that *L. patella* from the Fiji Islands produces a new family of novel thiazole-containing polyketide metabolites, the patellazoles A–C (**1–3**).[3] The patellazoles were potent cytotoxins in the NCI human cell line protocol with mean IC_{50}'s of 10^{-3}–10^{-6} μg/mL and antifungal against *Candida albicans*. Solvent partition of a MeOH extract of 220 g of freeze dried and pulverized *L. patella* resulted in concentration of activity in the CCl_4 fraction. Gravity column chromatography of this fraction on a silica gel 62 bed followed by successive RP and silica gel HPLC afforded 97 mg of **1**, 143 mg of **2**, and 313 mg of **3**. We now wish to report the structure determination of patellazole C (**3**) (spectral data and assignments for patellazoles A and B are provided in the Supplementary Material).

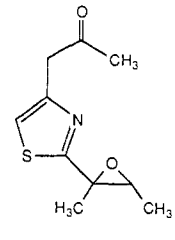
Patellazole C (**3**): $[\alpha]_D$ −100° (*c* 1.06, CH_2Cl_2); UV (MeOH) λ_{max} 241 nm (ε 26 000); IR (neat) ν_{max} 3474, 1728, 1708 cm^{-1} was



(1): R^1 = H; R^2 = H
(2) R^1 = H, R^2 = OH
(3) R^1 = OH; R^2 = OH

assigned molecular formula $C_{49}H_{77}NO_{13}S$ by FABMS mass measurement of the MH^+ ion (920.5179; requires 920.5197). All 49 carbons were visible in the ^{13}C NMR spectrum (Table I), and DEPT[4] experiments established the presence of 71 carbon bound protons (13 methyls, 6 methylenes, and 20 methines); D_2O exchange FABMS and ^1H NMR experiments indicated the presence of six active protons.

A double quantum filtered phase sensitive COSY[5] and a ^1H–^{13}C chemical shift correlation experiment[6] established all one bond ^1H–^{13}C connectivities and partial structures representing C3–C8, C10–C15, C16–C17, C18–C23, C25–C26, C32–C33, and C35–C37. The presence and position of an epoxy thiazole was indicated by NMR data (Table I) which compared favorably with 2-*tert*-butyl-4-methylthiazole.[7] The J_{CH} of 186.7 Hz for C29 is consistent with published data for thiazoles.[7] Similarly, the J_{CH} of 172.6 Hz for C32 is indicative of a small ring heterocycle. These assignments were confirmed by treatment of patellazole C with O_3 in CH_2Cl_2 followed by a reductive workup to give thiazole **4**.[8] These partial structures plus three carbonyls account for all sp^2 atoms indicating the remaining unsaturation must be a ring.



(4)

The connection of partial structures in **3** was established by a combination of INAPT,[9] COLOC,[10] and 2D INADEQUATE[11]

[†] Department of Medicinal Chemistry.
[‡] Department of Chemistry.

(1) Alfred P. Sloan Foundation Fellow, 1985–1989. NIH Career Development Awardee, 1987–1992.

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(3) The tunicate was identified as *Lissoclinum patella* (Gottschatt, 1898) by Dr. Francoise Monniot, Museum National d'Histoire Naturelle Paris, France.

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(7) (a) Babadjamian, A.; Metzger, J. *Bull. Soc. Chim. Fr.* **1968**, 4878. (b) Garnier, R.; Faure, R.; Babadjamian, A.; Vincent, E. J. *Bull. Soc. Chim. Fr.* **1972**, 1040: UV (MeOH) λ_{max} 246.3 nm (ε 4390); ^1H NMR (CCl_4) δ 6.52 (s, H5); ^{13}C (CCl_4) δ 178.9 (s, C2), 151.5 (s, C4), 111.4 (d, J_{CH} = 185.5 Hz, C5).

(8) UV (MeOH) λ_{max} 251 nm (ε 4200); ^1H NMR (C_6D_6) δ 6.46 (s, 1 H), 3.42 (dd, 2 H, *J* = 16.1 Hz), 2.82 (q, 1 H, *J* = 5.4 Hz), 1.73 (s, 3 H), 1.63 (s, 3 H), 0.88 (d, 3 H, *J* = 5.4 Hz); HREIMS, $C_{10}H_{13}NOS$ (obsd 211.0675, req. 211.0667).

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0002-7863/88/1510-7919$01.50/0

Table I. Patellazole C: ^1H and ^{13}C NMR Data

C no.	$^{13}C^a$ ppm (mult)^b		$^1H^c$ ppm (mult, J (Hz))
1	171.36 (s)		
2	81.25 (s)		
3	32.65 (t)	A	1.90 (bdd, 13.6, 4.4)
		B	2.62 (dd, 13.6, 4.4)
4	32.14 (t)	A	1.06 (m)
		B	1.44 (m)
5	28.17 (d)		1.85 (bm)
6	44.32 (t)	A	1.30 (ddd, 11.3, 11.3, 2.3)
		B	1.56 (dd, 11.3, 5.7)
7	72.56 (d)		3.87 (bm)
8	50.05 (d)		3.13 (dq, 9.5, 6.8)
9	216.43 (s)		
10	56.28 (d)		4.28 (ddd, 10.8, 7.6, 4.0)
11	124.85 (d)		5.22 (dd, 10.8, 10.8)
12	134.39 (d)		5.93 (dt, 10.8, 5.7)
13	32.37 (t)	A	1.53 (m)
		B	3.48 (dd, 12.1, 12.1)
14	38.86 (d)		1.95 (m)
15	74.32 (d)		3.68 (bd, 9.7)
16	69.44 (d)		3.90 (bd, 8.6)
17	87.01 (d)		4.09 (d, 8.6)
18	132.15 (s)		
19	133.36 (d)		6.38 (d, 10.8)
20	125.31 (d)		6.62 (dd, 15.3, 10.8)
21	136.14 (d)		6.30 (dd, 15.3, 5.6)
22	35.69 (d)		3.25 (m)
23	85.62 (d)		4.87 (d, 2.3)
24	75.38 (s)		
25	130.40 (d)		5.47 (s)
26	133.96 (s)		
27	34.68 (t)	A	3.52 (d, 13.4)
		B	3.83 (d, 13.4)
28	154.05 (s)		
29	114.21 (d)		6.26 (s)
30	174.76 (s)		
31	59.98 (s)		
32	65.00 (d)		2.73 (q, 5.4)
33	14.03 (q)		0.92 (d, 5.4)
34	175.39 (s)		
35	49.49 (d)		2.51 (dq, 9.0, 7.1)
36	69.29 (d)		3.85 (m)
37	20.36 (q)		1.11 (d, 6.5)
38	24.20 (q)		1.49 (s)
39	18.13 (q)		0.93 (d, 6.8)
40	13.52 (q)		0.82 (d, 6.8)
41	62.52 (t)	A	3.77 (dd, 10.8, 4.0)
		B	4.05 (bdd, 10.8, 7.6)
42	16.03 (q)		1.12 (d, 7.1)
43	56.01 (q)		3.26 (s)
44	10.99 (q)		2.00 (s)
45	19.08 (q)		1.60 (d, 7.1)
46	27.49 (q)		1.47 (s)
47	24.79 (q)		1.62 (fd, 1.1)
48	15.58 (q)		1.67 (s)
49	14.85 (q)		1.12 (d, 7.1)

[a] Measured at 125 MHz; referenced to C_6D_6 (128.0 ppm). [b] Multiplicity determined with DEPT experiment. [c] Measured at 500 MHz; referenced to C_6D_5H (7.15 ppm).

NMR experiments (Table I). INAPT connections from H3 and H38 to C1 and C2 plus INADEQUATE connection C38-C2-C3 confirmed placement of the ester carbonyl at 171.36 ppm as C1. Irradiation of H8 and H10 gave a signal at 216.43 ppm in the INAPT which indicated that C9 is a ketone and extended the carbon chain to C15. Although H15 failed to show vicinal coupling to H16, H17 showed connections to C15 in the INAPT and to C16 in the COLOC. The O-methyl exhibited an INAPT connection to C17, and both H15 and H16 sharpened in the D_2O exchange ^1H NMR spectrum, indicating that C15 and C16 bear secondary hydroxyls and C17 a methoxyl. Furthermore, the INADEQUATE data showed clear evidence for the sequence C15-C16-C17-C18, which effectively extends the carbon chain to C23. Both the COLOC and INAPT data showed strong correlation of H23 to the ester carbonyl at 171.36 ppm which was previously shown to be C1. This connection establishes a 24-membered macrolide. The proton on C23 showed further INAPT correlations to C24, C25 and C46, and H25 and H46 correlated to C24 in the COLOC. The remainder of the side chain was also established from long-range correlation data and was confirmed by isolation of **4**. Protons 35 and 49 correlated to the remaining carbonyl at 175.39 ppm confirming the presence of an α-methyl-β-hydroxy butyrate. The ester was attached at C2 based on deuterium exchanged ^{13}C NMR studies in which C7, C15, C16, C24, and C36 all exhibited upfield isotope induced shifts from 0.10 to 0.17 ppm, whereas C2, C17, and C23 showed negligible changes. This assignment was also substantiated by ^1H NMR data.

The patellazoles represent a new class of macrolides which incorporate an unusual thiazole moiety. A full paper discussing the chemistry and biological activity of all three members of this family is in preparation.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra, double quantum COSY, selected INAPT, and 2D INADEQUATE connections (23 pages). Ordering information is given on any current masthead page.

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Patellazole B: A Novel Cytotoxic Thiazole-Containing Macrolide from the Marine Tunicate *Lissoclinum patella*[1]

David G. Corley and Richard E. Moore*

Department of Chemistry, University of Hawaii at Manoa Honolulu, Hawaii 96822

Valerie J. Paul

Marine Laboratory, UOG Station Mangilao, Guam 96923

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Didemnid tunicates, marine chordates that are well-known for symbiotic associations with microscopic algae, produce a fascinating array of unusual natural products.[2] *Lissoclinum patella*, for example, produces several novel cyclic peptides characterized

(1) A preliminary account of this work was made at the 16th International Symposium on the Chemistry of Natural Products, IUPAC '88, Kyoto, Japan, May 29-June 4, 1988.

(2) The most important compounds discovered to date are the didemnins, potent cytotoxic and antiviral cyclic depsipeptides from Caribbean *Tridemnum solidum* [Rinehart, K. L., Jr.; Gloer, J. B.; Cook, J. C., Jr.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 1857]. Didemnin B is currently in Phase II clinical trials at the National Cancer Institute for the treatment of human cancer. For a current review, see: Rinehart, K. L., Jr.; Kishore, V.; Bible, K. C.; Sakai, R.; Sullins, D. W.; Li, K.-M. *J. Nat. Prod.* **1988**, *51*, 1.

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