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GONIODOMIN A, A NOVEL POLYETHER MACROLIDE FROM THE DINOFLAGELLATE GONIODOMA PSEUDOGONIAULAX

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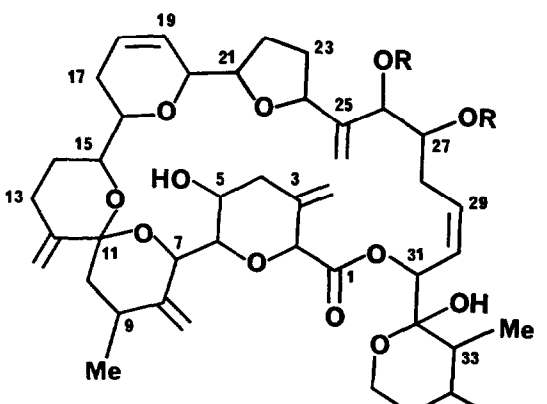
Summary: A novel antifungal polyether macrolide, goniodomin A, was isolated from the dinoflagellate Goniodoma pseudogoniaulax collected in the rock pool. Its structure was elucidated to be 1 on the basis of spectral data.

Dinoflagellates[1] and blue-green algae[2] have been well known to produce biologically and chemically interesting metabolites including toxins[3] and much attention has been paid to these microalgae. In 1968, Sharma et al.[4] reported the isolation of an antifungal compound, goniodomin, from the dinoflagellate Goniodoma sp. blooming in the bay near La Parguera, Peurto Rico, but its structure has remained unknown except for a few physical and chemical data. In the course of our studies on biologically active substances from microalgae, we found that the dinoflagellate Goniodoma pseudogoniaulax[5] showed a potent antifungal activity. We now describe the isolation and structural elucidation of goniodomin A, a novel polyether macrolide which is supposed to be closely related to goniodomin.

The dinoflagellate bloomed in the rock pool at Jogashima, Kanagawa Prefecture from June to July in 1986 and was collected by filtration with



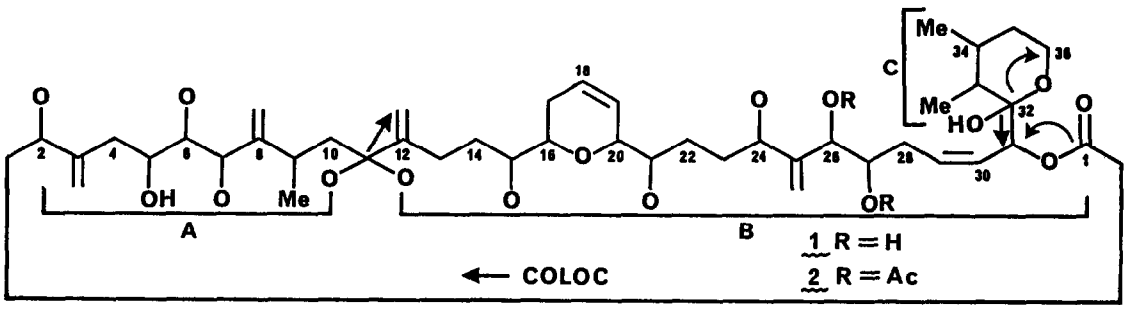
1 R = H
2 R = Ac

Table 1. ^{13}C and ^{1}H NMR Spectra of Goniodomin A

C	$\delta^{13}C^{a}(J_{C-H})$	$\delta^{1}H^{b}$	C	$\delta^{13}C^{a}(J_{C-H})$	$\delta^{1}H^{b}$
1	168.1s		19	129.1d(163)	6.277dddd
2	76.2d(140<)	4.309s	20	76.3d(140<)	4.390ddddd
3	139.7s		21	81.4d(150)	4.030dt
3=CH_2	112.1t(162)	4.779s	22	29.9t(128)	2.226ddd
		5.002s	23	31.4t(132)	1.55 m
4	40.7t(136)	2.331dd	23'		2.14 m
4'		2.820dd	24	79.1d(150)	5.203dd
5	70.2d(146)	4.133ddd	25	147.0s	
5-OH		4.455s	25=CH_2	113.4t(158)	5.039s
6	80.2d(142)	3.683dd			5.058s
7	73.1d(146)	5.133d	26	81.0d(145)	4.073d
8	148.6s		26-OH		3.08 or 3.85
8=CH_2	110.4t(158)[c]	4.933s	27	72.8d(145)	3.930ddd
		5.177s	27-OH		3.08 or 3.85
9	33.6d(122)	2.537ddq	28	31.8t(128)	2.14 m
9-Me	20.0q(125)	1.412d	28'		2.976dddd
10	44.1t(130)	1.730dd	29	135.1d(156)	6.453ddd
10'		2.095dd	30	123.3d(162)	5.866ddd
11	101.0s		31	73.5d(149)	5.962d
12	150.1s		32	97.5s	
12=CH_2	107.5t(157)[c]	4.675s	32-OH		2.797s
		4.933s	33	40.9d(124)	1.329ddq
13	27.5t(128)	1.948dd	33-Me	12.7q(126)	0.984d
14	25.4t(128)	1.17 m	34	30.8d(134)	1.664m
14'		1.33 m	34-Me	20.0q(125)	0.740d
15	76.0d(140<)	3.686ddd	35	34.2t(124)	1.17 m
16	76.5d(140<)	3.818ddd	36	60.6t(144)	3.560ddd
17	27.5t(128)	1.55 m	36'		3.902ddd
18	123.2d(164)	5.659ddd			

$J_{H,H}$ in Hz : 4,4'=13.3; 4,5=10.5; 4',5=5.3; 5,6=8.6; 6,7=8.6; 9,9-Me=6.8; 9,10=6.8; 9,10'=6.8; 10,10'=13.8; 13,14=10; 13,14'=4.4; 14,15=9.1; 14',15=6.7; 15,16=9.1; 16,17=9.1; 16,17'=4; 17,18=2; 17',18=2; 17,19=2; 17',19=2; 17,20=2; 17',20=2; 18,19=10.3; 18,20=2; 19,20=2; 20,21=9.4; 21,22=7; 22,23=7; 22,23'=4.7; 23,24=9.9; 23',24=4.8; 26,27=6.3; 27,28=10.2; 27,28'=1.9; 28,28'=12.8; 28,29=3.7; 28',29=10.8; 28',30=1.4; 29,30=10.8; 30,31=10.5; 32-OH,33=1.0; 33,33-Me=6.5; 33,34=5.1; 34,34-Me= 6.5; 36,36'=11

a: Measured in $CDCl_3$ (100MHz), b: in C_6D_6 (400MHz).
c: Assignments may be interchanged.



Scheme 1

plankton nets. The ethanol and methanol/dichloromethane (1:1) extract of the wet cells (320g) was partitioned between water and ether. The organic layer was subjected to column chromatography on silica gel [benzene/ethyl acetate (8:2, 7:3)] and ODS (85% methanol), followed by reversed phase HPLC (YMC-ODS, 85% methanol) to give goniodomin A (**1**, 180mg, 0.05% yield), which showed antifungal activity against Mortierella ramannianus and Candida albicans at a concentration of 0.5μg/ml, and inhibited the cell division of fertilized sea urchin eggs at 0.05μg/ml.

Goniodomin A(**1**),$[\alpha]_D^{20}$+28°(c 0.13, MeOH), has no UV absorption maximum above 210nm and its IR spectrum indicated the presence of hydroxyl (3430 cm^{-1}) and ester (1760 cm^{-1}) groups. ^{13}CNMR (Table 1) revealed 43 carbons, which were assigned to one carbonyl, two disubstituted olefins, four exomethylenes, two acetals, twelve oxymethines, one oxymethylene, nine methylenes, three methines, and three methyls by DEPT data. These data and SIMS [m/z 874 $(M+DEA+H)^+$] together with combustion data led to the molecular formula $C_{43}H_{60}O_{12}$ (Anal. Found: C,67.04%; H,7.81%, Calcd. C,67.19%; H,7.81%). This compound was suggested to have four hydroxyl groups from its ^{1}HNMR (Table 1) and yielded diacetate(**2**) [FABMS m/z 958 $(M+DEA+H)^+$].

The detailed analyses of H-H COSY and C-H COSY spectra of **1** allowed us to deduce partial structures **A-C** as shown in Scheme 1. As to partial structure **A** (C-2 to C-10), the exomethylene protons on C-3 and C-8 showed obvious cross peaks due to couplings with the allylic protons (H-2 and H-4; H-7 and H-9) in the H-H COSY spectrum. The signal for 5-OH showed a cross peak due to coupling with the oxymethine proton H-5, but this hydroxyl group resisted acetylation. The H-31 signal (partial structure **B**; C-12 to C-31) was at fairly low field(δ5.962) for an oxymethine proton, strongly suggesting that C-31 attaches to the ester oxygen on C-1. The geometry of $\Delta^{18,19}$ and $\Delta^{29,30}$ -double bonds was determined to be Z by the coupling constant ($J_{18,19}$=10.3Hz and $J_{29,30}$=10.8Hz). The H-20 proton was vicinally, allylically, and homo-allylically coupled with H-19, H-18, and H-17, respectively, indicating that the dihydropyran is formed between C-16 and C-20 as in the case of scytophycins.[6] It was supported by the fact that the NOE was seen between H-16 and H-20 in PSNOESY spectrum.[7] As to partial structure **C**(C-32 to C-36), the hemiacetal carbon C-32 was suggested to be connected to C-33 since the signal 32-OH was clearly coupled with H-33 ($J_{32\text{-}OH,33}$=1Hz). This was also supported by the fact that the obvious cross peaks were observed between C-32 and 32-OH and between C-32 and 33-Me in the COLOC spectrum(6Hz).[8] Partial structures **A-C** and the remained acetal carbon C-11 were connected by COLOC spectrum as shown in Scheme 1. The signal for H-2 showed a cross peak due to coupling with the ester carbonyl carbon C-1. This observation indicates that C-1 connects to C-2. The remained acetal carbon C-11 must be attached to C-12 since the cross pesks were observed between C-11 and exomethylene protons on C-12. Connectivity of this acetal carbon to C-10 was deduced from the fact

that the methylene protons on C-10 were coupled with only H-9 in the ^{1}HNMR spectrum and C-11 was the last quaternary carbon to block the methylene group. In COLOC spectrum, C-32 showed obvious cross peaks due to couplings with oxymethylenes H-36 and 36', indicating the presence of tetrahydropyran (C-32 to C-36). Analysis of the H-H COSY spectrum of diacetate **2**[9] showed that the signals of two hydroxy methine protons (H-26, H-27) were shifted to lower field (H-26; δ3.390 to 5.55, H-27; δ4.073 to 5.95). This fact confirmed that the two remained hydroxyl groups should be located on C-26 and C-27. Finally, the positions of ether linkages were decided by PSNOESY spectrum. The NOE between H-2 and H-6 confirmed the formation of a tetrahydropyran (C-2 to C-6). Observation of NOEs (9-Me and H-15, H-7 and H-15) supported the positions of ether linkages of C-7 to C-11 and C-11 to C-15. Although no NOE was observed between H-21 and H-24, suggesting that these protons are trans, the remained oxygen was necessarily connected to C-21 and C-24 from the consideration of their chemical shifts in the ^{13}CNMR spectrum.

Goniodomin A is a unique polyether macrolide, and structurally resembles pectenotoxin obtained from the digestive gland of scallop.[10] Studies on the stereochemistry and other minor components are under progress.

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