A New Cyclic Peptide, Ascidiacyclamide, isolated from Ascidian

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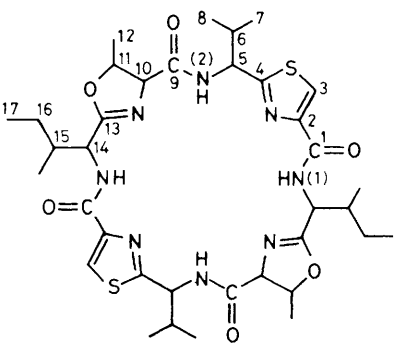
A new cytotoxic cyclic peptide, ascidiacyclamide, has been isolated from ascidian and its structure has been elucidated by n.m.r. spectroscopy.

Several cytotoxic cyclic peptides isolated from marine invertebrates have been reported.[1-4] Here we report the structural elucidation of a new cytotoxic cyclic peptide, ascidiacyclamide (**1**),† isolated from an unidentified species of ascidian which was collected from Rodda Reef, Queensland, Australia.

The ethanol extact of the lyophilized sample was chromatographed through silica gel columns and the fractions were assayed on cultured cells; two active constituents, ascidiacyclamide (**1**) and ulithiacyclamide (**2**),[1] were isolated. Ascidiacyclamide (**1**)‡ was obtained as colourless prisms from benzene: m.p. 139—139.5 °C, *m/z* 756 (M^+) and 713 ($M^+ - CHMe_2$), $[\alpha]_D^{25}$ +164° (*c* 0.466, $CHCl_3$), λ_{max} (MeOH) 232 nm (ε 21 000), ν_{max} (film) 3380, 3340, 1680, and 1652 cm^{-1}. Owing to the symmetric structure, only 18 ^{13}C n.m.r. signals and 26 ^1H n.m.r. signals were observed (see Table 1). The cyclic peptide structure of ascidiacyclamide (**1**) was suggested by i.r. spectroscopy and its lipophylic nature; acid hydrolysis gave a 1 : 1 : 1 ratio of isoleucine, threonine, and another hydrolysate.



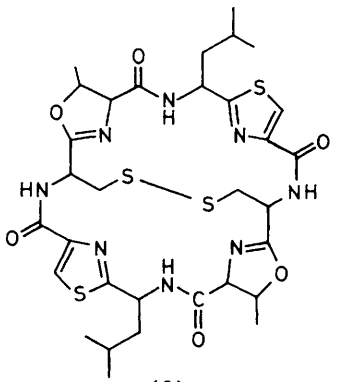
(**1**)

† The compound has a strong lethal effect on PV_1 cultured cells transformed with polyoma virus; T/C 100% was observed at 10 μg/ml.

‡ Satisfactory elemental analyses were obtained.

Table 1. ^{13}C N.m.r. (25 MHz) and ^{1}H n.m.r. (100 MHz except 16-H's) spectra of ascidiacyclamide (**1**), 16-H's were recorded at 360 MHz; [protons correlated by decouplings.

Position	^{13}C ($CDCl_3$) δ/p.p.m.	^{1}H ($CDCl_3$) δ
1	171.2	
2	160.3	
3	123.0	7.91 (1H,s)
4	149.5	
5	54.7	5.22 (1H, dd, *J* 6.3, 10.0 Hz)
6	33.4	2.31 (1H, dqq, *J* 6.3, 6.1, 6.1 Hz)
7	19.1	1.07 (3H, d, *J* 6.1 Hz)
8	17.9	1.13 (3H, d, *J* 6.1 Hz)
9	168.9	
10	73.5	4.27 (1H, dd, *J* 6.3, 1.2 Hz)
11	81.5	4.86 (1H, dq, *J* 6.3, 6.3 Hz)
12	21.7	1.49 (3H, d, *J* 6.3 Hz)
13	168.4	
14	52.0	4.83 (1H, ddd, *J* 8.1, 6.1, 1.2 Hz)
15	37.0	1.95 (1H, m)
16	24.6	1.17 (1H, m)
		1.27 (1H, m)
17	10.7	0.72 (3H, dd, *J* 6.8, 6.8 Hz)
18	14.9	0.80 (3H, d, *J* 6.8 Hz)
N(1)		8.01 (1H, d, *J* 8.1 Hz)
N(2)		7.40 (1H, d, *J* 10.0 Hz)



(**2**)

The ^{1}H n.m.r. signals of the isoleucine and threonine moieties were all assigned by decoupling studies (Table 1). The homoallylic coupling between 10-H and 14-H shows the existence of an oxazoline ring[1,5] which is formed by condensation of isoleucine and threonine. The remaining moiety was shown to be a thiazole ring with a valine side-chain by ^{13}C and ^{1}H n.m.r. spectroscopy. The substitutions on the thiazole ring were determined by the ^{13}C n.m.r. chemical shifts at 160.3 (s), 149.5 (s), and 123.0 (d) p.p.m. and the ^{1}H n.m.r. chemical shift at 7.91 (s); the chemical shifts are quite similar to those reported for the thiazole ring in ulicyclamide.[1]

The relation between the isoleucine–threonine part and the thiazole ring with a valine side-chain was elucidated by the use of a long range selective proton decoupling technique. The ^{13}C n.m.r. signal at δ 168.9 (m, C-9) p.p.m. was simplified by irradiation of the ^{1}H n.m.r. signal at δ 5.22 (5-H) in order to determine the relation between 5-H and C-9. The ^{13}C n.m.r. signal at δ 171.2 (ddd, *J* 3.7, 5.1, and 8.1 Hz, C-1) p.p.m. was changed to a double doublet signal (*J* 3.7 and 8.1 Hz) by irradiation of the ^{1}H n.m.r. signal at δ 4.83 (14-H) in order to determine the relation between C-1 and 14-H.

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