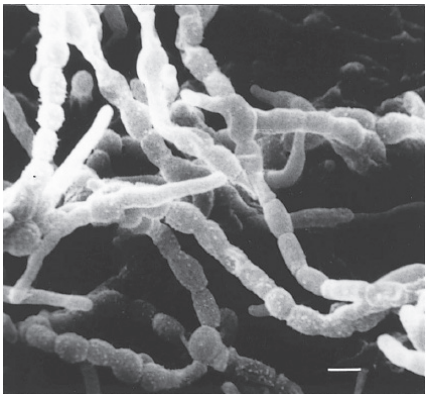
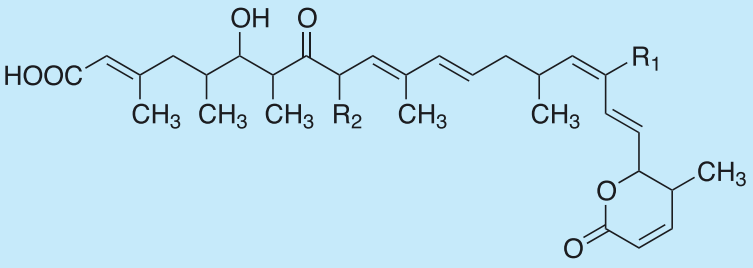
Kazusamycin ©

1. Discovery, producing organism and structures[1-5,7,8)]

Kazusamycins were isolated from the culture broth of the actinomycete strain 81-484 and found to be antitumor compounds. The physico-chemical and biological characteristics of kazusamycins were similar to leptomycins. The first total synthesis of kazusamycin A was achieved by Kuwajima *et al*.[10)]



Streptomyces sp. 81–484



	R_1	R_2
Kazusamycin A	CH_2CH_3	CH_2OH
Kazusamycin B	CH_3	CH_2OH
Leptomycin A	CH_3	CH_3
Leptomycin B	CH_2CH_3	CH_3

2. Physical data (Kazusamycin A)[1)]

Pale yellow sticky oil. $C_{33}H_{48}O_7$; mol wt 556.34. Sol. in MeOH, EtOH, EtOAc, acetone, benzene, $CHCl_3$, Et_2O. Insol. in hexane, H_2O.

3. Biological activity[1,3,6,7)]

1) Antitumor activity of kazusamycin A on P388 leukemia and sarcoma 180[1)]

Dose (mg/kg/day x day)	P388		Sarcoma 180	
	MS	ILS (%)	MSD	ILS (%)
control	12	0	12	0
0.008 x 5	16	33	22	83
0.016 x 5	19	58	28	133
0.031 x 5	NT	NT	20	67

P388 leukemia cells and sarcoma 180 cells were inoculated i.p. into CDF1 mice and ICR mice, respectively. Mice were given i.p. with kazusamycin A on days 1-5. Antitumor activity was evaluated by the increase of life span (ILS); (T/C-1) x 100%, where T was the median survival days (MSD) of the treated group and C was the MSD of the control group. NT; not tested.

2) Cytotoxicity of kazusamycin A[1)]

Kazusamycin A was effective in completely preventing growth of HeLa cells at a concentration of 3.3 ng/ml.

3) Antimicrobial activity of kazusamycins[3)]

Kazusamycins were active against *Schizosaccharomyces pombe* and *Rhizopus javanicus*, but inactive against Gram-positive bacteria, Gram-negative bacteria, and the following microorganisms: *Saccharomyces cerevisiae*, *Candida albicans*, *Aspergillus fumigatus*, *Rhodotorula rubra* and *Trichophyton mentagrophytes*.

	MIC (μg/ml)	
Test organism	Kazusamysin B	Kazusamysin A
Schizosaccharomyces pombe IAM 4863	0.03	0.05
Rhizopus javanicus IAM 6241	0.78	3.13

4) Cell cycle[6)]

Kazusamycin B arrested synchronized L1210 cells in the G1 phase at 4 hours. When the cells were exposed to the drug longer than 12 hours, an unidentified cell population with lower fluorescence intensity than the G1 population was observed.

5) Nuclear export[7-9)]

Kazusamycins and leptomycins were found to be inhibitors of the nucleo-cytoplasmic translocation of the HIV-1 Rev protein at nM concentrations. Leptomycin B has been indicated to inhibit the nuclear export signal (NES)-dependent nuclear export of proteins by CRM1.

4. References

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