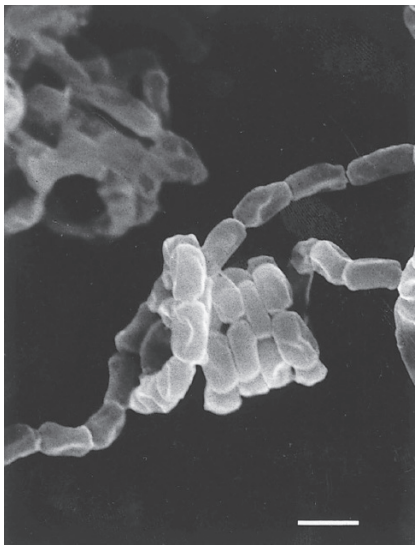
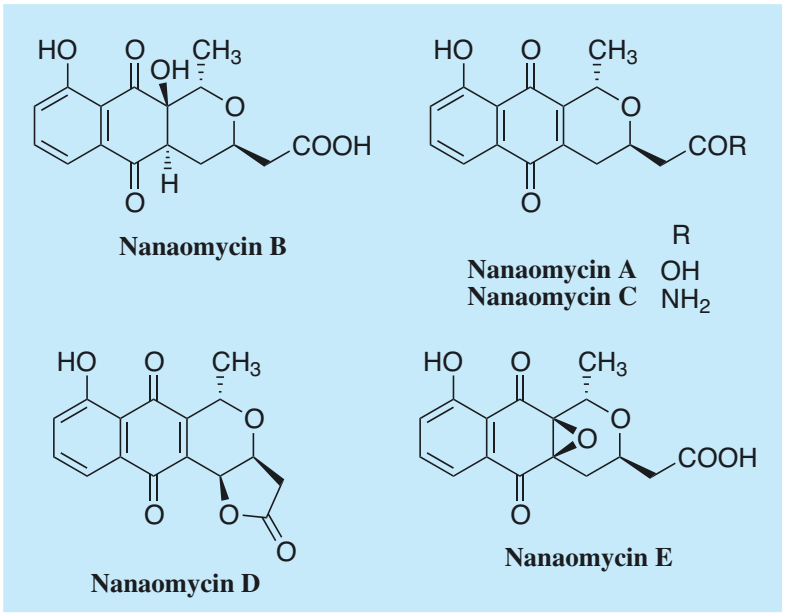
Nanaomycin©

1. Discovery, producing organism and structures[1-6)]

While screening for antibiotics more active against *Mycoplasma gallisepticum* than against bacteria, nanaomycins A, B, C, D and E were isolated from the culture broth of the actinomycete strain OS-3966^T. Nanaomycin A was found to possess potent inhibitory activity against fungi. Nanaomycin A inhibited *in vitro* growth of the human malaria parasite *Plasmodium falciparum* with an IC_{80} value of 33.1 nM[7)]. The total syntheses of nanaomycins have been reported by many groups. The first total synthesis of nanaomycins A and D was reported by Li *et al*.[8)] (See Appendix-I).



Streptomyces rosa subsp. *notoensis* OS-3966^T

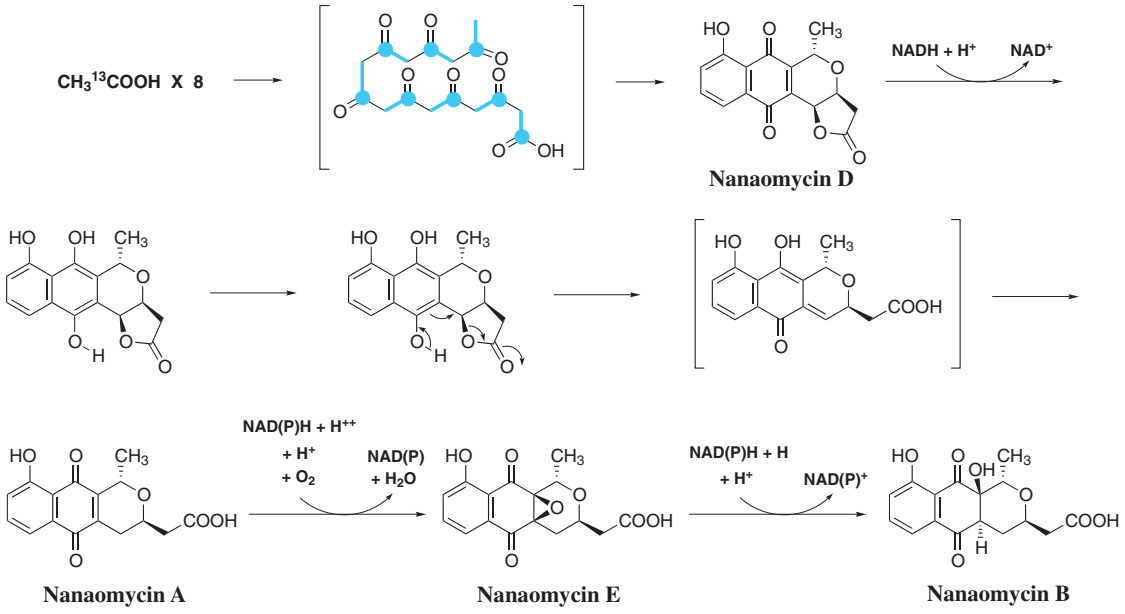


2. Physical data (Nanaomycin A)

Orange needles. $C_{16}H_{14}O_6$; mol wt 302.08. Sol. in MeOH, EtOH, $CHCl_3$, EtOAc.

3. Biosynthesis[3,9-12)]

Nanaomycins are biosynthesized from eight acetate units *via* "polyketide" and are converted to D→A→E→B by enzymatic and nonenzymatic systems.



4. Biological activity[1,2,4,14,15)]

1) Antimicrobial activity of nanaomycin A[1,2,4)]

Test organism	MIC(μg/ml)*
Bacillus subtilis PCI219	7.8
Staphylococcus aureus FDA209P	3.9
Escherichia coli NIHJ	31.3
Candida albicans	31.2
Aspergillus fumigatus IAM 2612	12.5
Microsporum gypseum 704	0.8
Trichophyton interdigitale	1.6
T. mentagrophytes	0.8
T. rubrum	0.1
T. schroenleini	0.2
Mycoplasma gallisepticum KP-13	0.05
M. gallisepticum 333P (spiramycin resistant)	<0.013

*Nutrient agar for bacteria (pH 7.0, 2 days, 37˚C),
Potato-glucose agar for fungi (pH 6.4, 4 days, 27˚C),
Eiken PPLO agar for mycoplasmas (pH 7.8, 8 days, 37˚C)

2) Therapeutic effect of nanaomycin A against *Trichophyton mentagrophytes* infection in guinea pigs[13)]

Treatment*	Macroscopic Discoverys**		Animals yielding negative cultures (number/total)		
	Erythema	Scale	4 days	7 days	14 days
Untreated	++	++	0/12	0/12	0/12
Nanaomycin A, 1%	±	±	12/12	9/12	6/12
Nanaomycin A, 2%	±	±	12/12	8/12	7/12

* Treatment began 2 days after infection and was administered once daily for 8 days.
** Macroscopic Discoverys were graded on a basis of – to +++, depending on the degree of erythema, scaling, and hair growth.

3) Mode of action[14,15)]

The quinone antibiotics, nanaomycins, are reduced by the respiratory chain-linked NADH or flavin dehydrogenase of the organism. The reduced forms of nanaomycins are quickly autooxidized by molecular oxygen producing O_2^-. The ability to produce O_2^- is related to the antimicrobial activity of nanaomycins.

5. Nanaomycin is commercially available as an antifungal agent for animals.

6. References

1. [74] S. Ōmura *et al*., *J. Antibiot*. **27**, 363-365 (1974)
2. [96] H. Tanaka *et al*., *J. Antibiot*. **28**, 860-867 (1975)
3. [97] H. Tanaka *et al*., *J. Antibiot*. **28**, 868-875 (1975)
4. [100] H. Tanaka *et al*., *J. Antibiot*. **28**, 925-930 (1975)
5. [109] S. Ōmura *et al*., *J. Chem. Soc*., *Chem. Commun*. 320-321 (1976)
6. [157] M. Kasai *et al*., *J. Antibiot*. **32**, 442-445 (1979)
7. [730] Y. Tanaka *et al,. J. Antibiot*. **52**, 880-888 (1999)

8. T. T. Li *et al., J. Am. Chem. Soc.* **100**, 6263-6265 (1978)
9. [184] C. Kitao *et al., J. Antibiot.* **33**, 711-716 (1980)
10. [211] S. Ōmura *et al., J. Biochem.* **90**, 291-293 (1981)
11. [212] S. Ōmura *et al., J. Biochem.* **90**, 355-362 (1981)
12. [251] H. Tanaka *et al., J. Antibiot.* **35**, 1565-1570 (1982)
13. [197] K. Kitaura *et al., Jpn. J. Antibiot.* **33**, 728-732 (1980)
14. [196] H. Marumo *et al., J. Antibiot.* **33**, 885-890 (1980)
15. [247] H. Hayashi *et al., J. Antibiot.* **35**, 1078-1085 (1982)