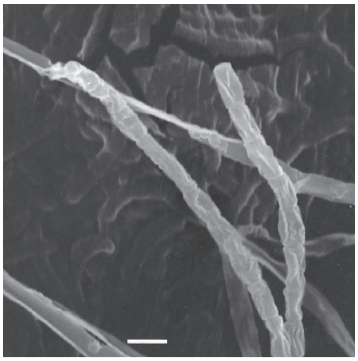
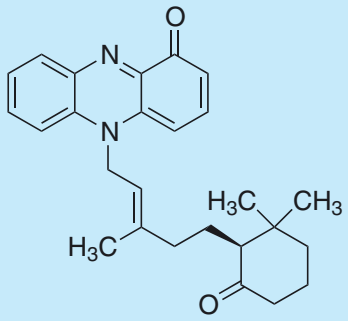
Phenazinomycin

1. Discovery, producing organism and structure[1)]

Phenazinomycin was isolated from the culture broth of the actinomycete strain WK-2057 while screening for antitumor substances using Sarcoma 180 tumor cells. The total synthesis of phenazinomycin was reported by Kitahara *et al*.[2)] (See Appendix-I).



Streptomyces sp. WK-2057



Phenazinomycin

2. Pysical data

Colorless needles. $C_{26}H_{30}N_2O_2$; mol wt 402.23. Sol. in MeOH, acetone, EtOAc. Insol. in H_2O, hexane.

3. Biological activity[1,3,4)]

1) Antimicrobial activity

Test organism	MIC (μg/ml)
Staphylococcus aureus KB 210	12.5
S. aureus FDA 209P	25.0
Bacillus subtilis KB 211	6.3
B. cereus KB 143	1.6
Micrococcus luteus KB 212	3.1
Mycobacterium smegmatis KB 42	> 100
Salmonella typhimurium KB 20	> 100
Pseudomonas aeruginosa KB 115	> 100
Candida albicans KF 1	> 100
Saccharomyces cerevisiae KF 237	> 100
Microsporum gypseum KF 64	50.0
Trichophyton mentagrophytes T-5 KF 213	100
Botrytis cinerea KF 241	100
Sclerotinia cinerea KF 181	25.0
Pyricularia oryzae KF 180	12.5

2) Antitumor activity

Dose (mg/kg/day)	MSD (range)	ILS (%)	Mean body weight (g) (day-9)
Saline	10.1 (9-12)	0	35.2 ± 2.4
2.8	14.4 (9-19)	43	32.5 ± 3.0
5.6	13.5 (9-20)	34	31.1 ± 4.3
11.1	20.3 (13-25)	101	27.9 ± 2.3
22.2	24.2 (21-33)	140	26.1 ± 0.9

Sarcoma 180 cells (1 x 10^6) were inoculated into ICR mice.
Mice were administered with phenazinomycin *i.p.* on days 1-9.

3) Antitrypanosomal activity

Phenazinomycin showed antitrypanosomal activity against GUTat 3.1 strain with IC_{50} of 230 ng/ml.[4)]

4. Biosynthesis[5)]

The biosynthetic gene cluster for phenazinomycin was identified from *Streptomyces iakyrus* DSM 41873, a producer of actinomycin G2-G6 and the biosynthetic pathway was proposed. The mutant of *acmG5'* gene, which is responsible for methylation to form 4-methyl-3-hydroxyanthranilic acid in actinomycin biosynthesis, enhanced phenazinomycin production and lost actinomycin G. Chorismate is a common precursor of the biosynthetic pathways for these two compounds.

5. References

1. [418] S. Funayama *et al*., *Tetrahedron Lett*. **30**, 3151-3154 (1989)
2. Y. Kinoshita *et al*., *Tetrahedron Lett*. **38**, 4993-4996 (1997)
3. [419] S. Funayama *et al*., *J*. *Antibiot*. **42**, 1037-1042 (1989)
4. [1072] K. Otoguro *et al*., *J*. *Antibiot*. **63**, 579-581 (2010)
5. Z. Qin *et al*., *FEMS Microbiol*. *Lett*. **352**, 62–68 (2014)