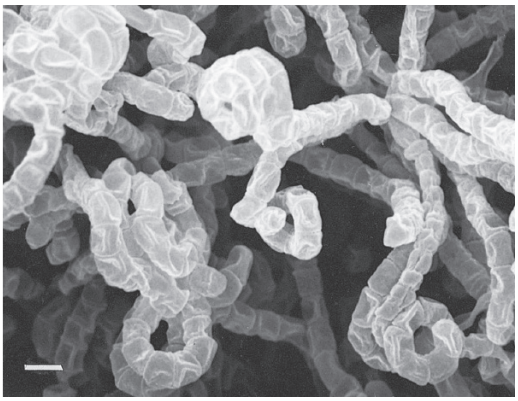
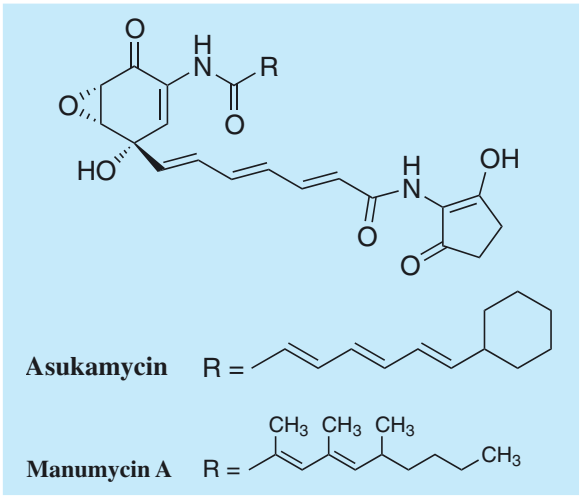
Asukamycin

1. Discovery, producing organism[1] and structure[2,3]

Asukamycin was isolated from the culture broth of *Streptomyces nodosus* strain AM-1042^T and recognized as an antibiotic. Asukamycin is related to the manumycin group antibiotics because it contains a multifunctional mC$_7$N unit as its central structural element, but has a naturally unique mono-substituted cyclohexane.



Streptomyces nodosus.
subsp. *asukaensis* AM-1042^T



2. Physical data[1]

Yellow needles. $C_{31}H_{34}N_2O_7$; mol wt 546.24. Sol. in DMSO, MeOH, acetone; Insol. in H_2O, hexane.

3. Biological activity[1]

The manumycin group antibiotics exhibit antibacterial activity against Gram-positive bacteria. In particular, asukamycin was found to have anticoccidial activity. These compounds are known to inhibit the protein farnesyltransferase[4].

Antimicrobial spectrum of asukamycin

Test organism	MIC (μg/ml)
Staphylococcus aureus FDA209 JC-1	0.78
Staphylococcus aureus FDA209	3.12
Staphylococcus aureus FS-1277*	6.25
Staphylococcus aureus KB-64**	6.25
Staphylococcus albus	12.5
Bacillus subtilis PCI 219	3.12
Bacillus subtilis ATCC6633	6.25
Bacillus megaterium APF	6.25
Bacillus anthracis	12.5
Bacillus cereus T	3.12
Bacillus agri	12.5
Micrococcus luteus PCI1001	6.25
Micrococcus flavus 16	1.56
Corynebacterium paurometabolum	1.56
Nocardia asteroides	1.56
Micobacterium smegmatis ATCC607	>100
Escherichia coli NIHJ	100
Klebsiella pneumoniae PCI602	>100
Salmonella typhimurium	>100
Shigella sonnei E-33	>100
Pseudomonas aeruginosa P-3	>100

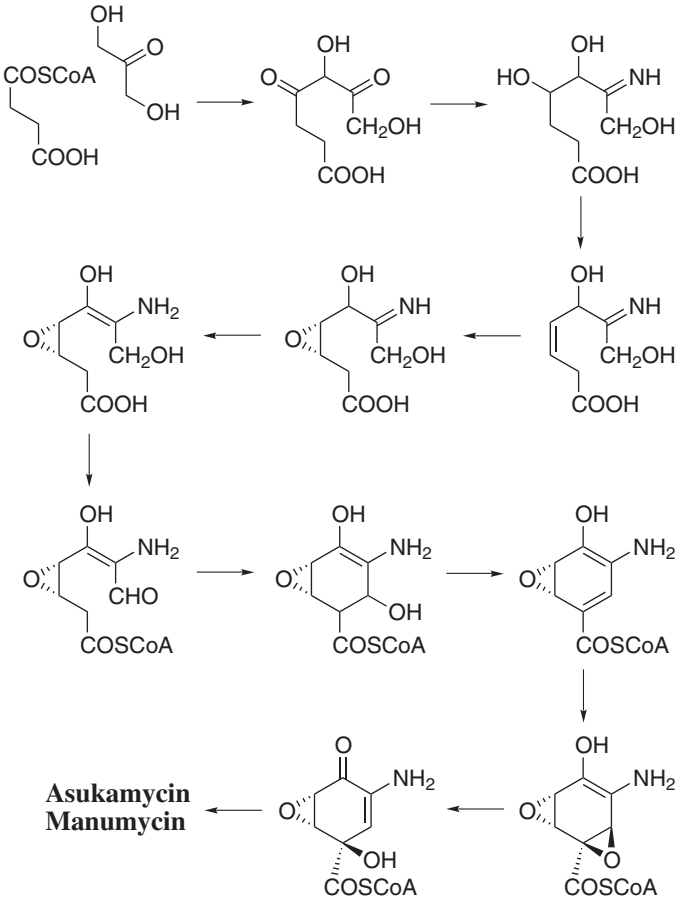
* resistant to penicillin
** resistant to tetracycline and erythromycin

4. Biosynthesis[5-16)]

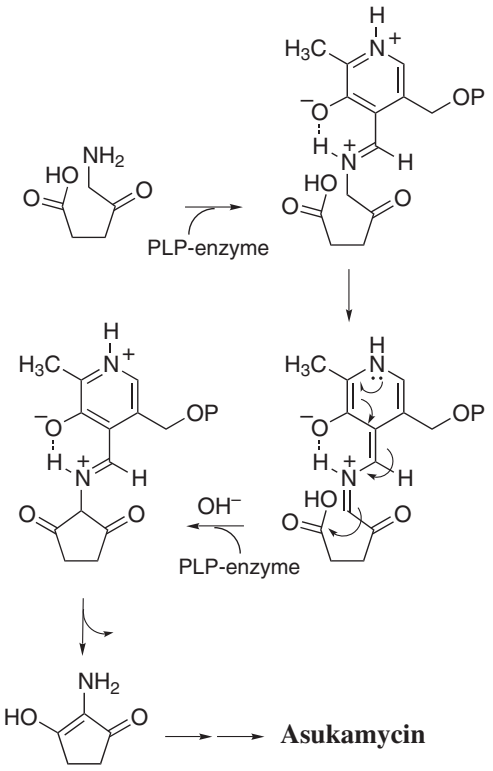
The central and multifunctional mC_7N unit typical of this group of antibiotics serves as the starting unit for a short polyketide chain. It is biosynthesized from a C_4 Krebs cycle and a C_3 triose phosphate pool, and is recognized to intermediate by a pathway distinct in nature from the shikimate, polyketide, or pentose phosphate routes leading to other mC_7N units.

The C_5 unit arises from a novel intermoleculular cyclization of 5-amino-levulinic acid, and a cyclohexane ring and the adjacent carbon arises from the seven carbon atoms of shikimic acid. The side chains represent typical polyketide-derived moieties, differing with respect to their combinations of starter and elongation units.

The biosynthetic gene cluster for asukamycin was identified. The biosynthetic pathway and transcriptional regulation were proposed.



Proposed pathway for assembly of mC_7N units[7)]



Model for assembly of C_5N units in asukamycin biosynthesis[7)]

5. References

1. [112] S. Ōmura *et al*., *J*. *Antibiot*. **29**, 876-881 (1976)
2. [160] K. Kakinuma *et al*., *J*. *Am*. *Chem*. *Soc*. **101**, 3402-3404 (1979)
3. H. Cho *et al*., *J*. *Org*. *Chem*. **58**, 7925-7928 (1993)
4. M. Hara *et al*., *Proc*. *Natl Acad*. *Sci*. *USA* **90**, 2281-2285 (1993)
5. [444] R. Thiericke *et al*., *J*. *Am*. *Chem*. *Soc*. **112**, 3979-3987 (1990)
6. [334] A. Nakagawa *et al*., *J*. *Chem*. *Soc*. *Chem*. *Commun*. 519-521 (1985)
7. [398] J. M. Beale *et al*., *J*. *Am*. *Chem*. *Soc*. **110**, 4435-4437 (1986)
8. K. Petrícková *et al*., *Chembiochem*. **15**, 1334-1345 (2014)
9. T. Ito, *Yakugaku Zasshi* **133**, 1007-1015 (2013)
10. Z. Rui *et al*., *Chem*. *Biol*. **20**, 879-887(2013)
11. L. Bai, *Chem*. *Biol*. **20**, 859-860 (2013)
12. P. Xie *et al*., *Appl*. *Microbiol*. *Biotechnol*. **96**, 451-460 (2012)
13. S. Pospíšil *et al*., *J*. *Appl*. *Microbiol*. **111**, 1116-1128 (2011)
14. Z. Rui *et al*., *J*. *Biol*. *Chem*. **285**, 24915-24924 (2010)
15. M. Petrícek *et al*., *J*. *Bacteriol*. **188**, 5113-5123 (2006)
16. Y. Hu & H. G. Floss, *J*. *Am*. *Chem*. *Soc*. **126**, 3837-3844 (2004)