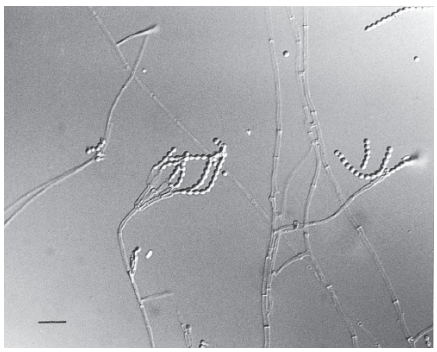
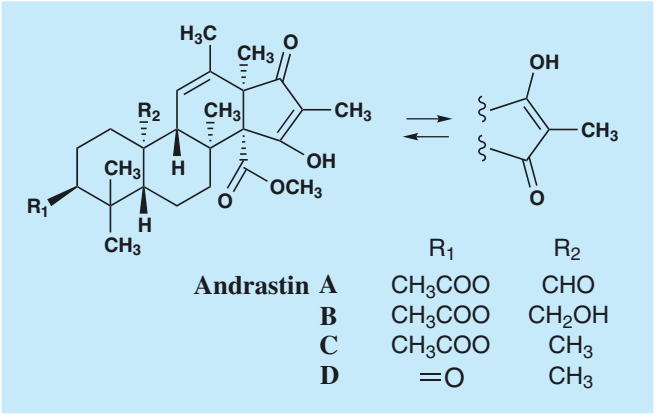
Andrastin ©

1. Discovery, producing organism and structures[1-4)]

Andrastins were isolated from the culture broth of a *Penicillium simplicissimum* strain FO-3929 and found to be protein farnesyltransferase inhibitors. The absolute configuration of the *p*-bromobenzoyl derivative of andrastin A was elucidated by X-ray crystallographic analysis and its skeleton was identified as *ent*-5α,14β-androstane.



Penicillium sp. FO-3929
(*Penicillium simplicissimum* FO-3929)
Bar: 20 μm



		R_1	R_2
Andrastin	**A**	CH_3COO	CHO
	B	CH_3COO	CH_2OH
	C	CH_3COO	CH_3
	D	=O	CH_3

2. Physical data (Andrastin A)

White powder. $C_{28}H_{38}O_7$; mol wt 486.60. Sol. in DMSO, MeOH, $CHCl_3$. Insol. in H_2O, hexane.

3. Biological activity[2,4,5)]

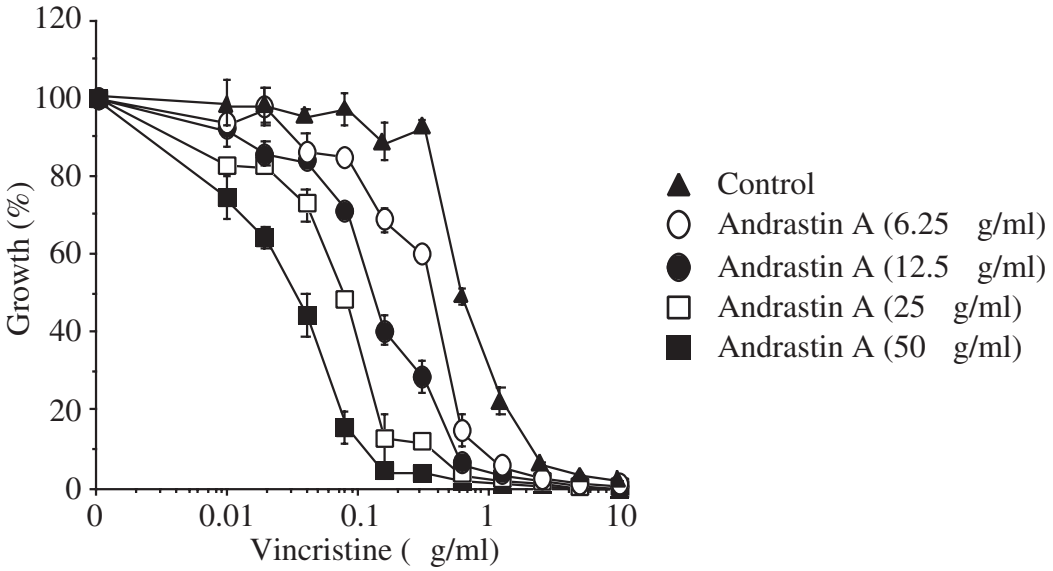
1) Inhibition of protein farnesyltransferase[2,4)]

Protein farnesyltransferase catalyzes the post-translational modification of ras p21 that is obligatory for cell transformation of this oncogene protein.

		IC_{50} (μM)
Andrastin	A	24.9
	B	47.1
	C	13.3
	D	25.7

2) Enhancement of drug accumulation in vincristine-resistant KB cells[5)]

Andrastin A enhanced the cytotoxicity of vincristine 1.5–20 fold in vincristine-resistant KB cells (VJ-300).



3) Other biological activity[2)]

No antimicrobial activity was shown at a concentration of 1,000 μg/ml against *Xanthomonas oryzae* KB88, *Candida albicans* KF-1, *Saccharomyces cerevisiae* KF26, *Mucor racemosus* KF223 (IFO 4581), *Pyricularia oryzae* KF180, *Aspergillus niger* KF 103 (ATCC 6275), *Staphylococcus aureus* KB34 (FDA 209P), *Bacillus subtilis* KB27 (PCI 219), *Escherichia coli* KB8 (NIHJ), *E. coli* KB176 (NIHJ JC-2), *Pseudomonas aeruginosa* KB105 (P3), *Micrococcus luteus* KB40 (PCI 1001), *Bacteroides fragilis* KB169, *Mycobacterium smegmatis* KB42 (ATCC607), or *Acholeplasma laidlawii* KB174 (PG8).

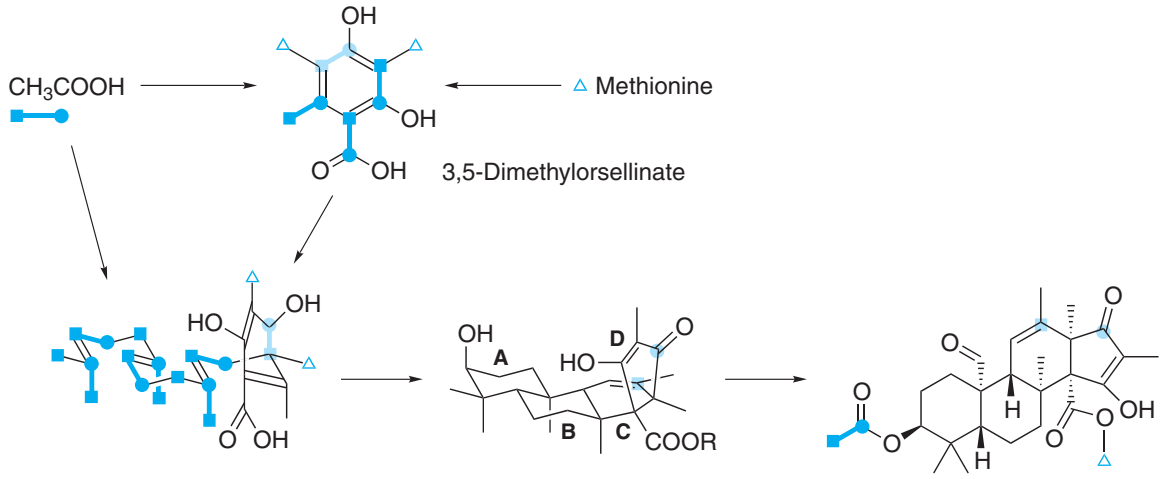
4. Biosynthesis[3, 7)]

The incorporation study of single and double labeled acetate into andrastin A and the result of a biosynthetic study of citreohybridonol, an analog of andrastins, conducted by Kosemura *et al.*,[6)] suggested that andrastins were synthesized as shown below.

A sesquiterpene, synthesized from farnesyl pyrophosphate, is cyclized to form an enantiomer of drimane. 3,5-Dimethylorsellinate derived from tetraketide is combined with drimane to form ring C. Ring D changes from cyclohexane to cyclopentane by a rearrangement. Thus, an enantiomer of the 5α,14β-androstane skeleton is formed.

Though many compounds produced by fungi from farnesylate and orsellinate have been reported, their absolute structures have not been elucidated. The absolute structures may therefore be different from the reported ones.

The biosynthetic gene cluster for andrastin was identified by Matsuda *et al.*[7)]



5. References

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6. S. Kosemura *et al.*, *J. Chem. Soc., Perkin Trans. 1* **1994**, 135-139 (1994)
7. Y. Matsuda *et al.*, *Tetrahedron* **69**, 8199-8204 (2013)