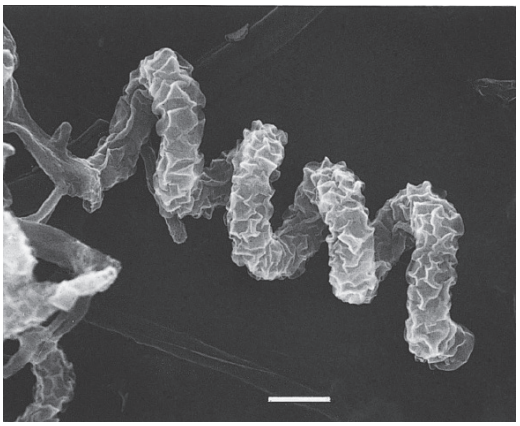
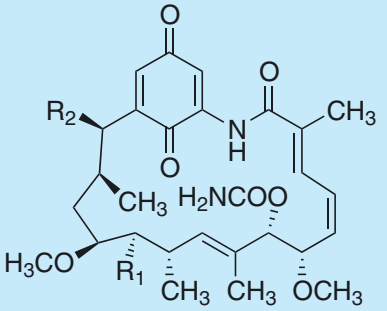
Herbimycin ©

1. Discovery[1], producing organism[1] and structures[2-7]

Herbimycins, new benzoquinoid ansamycin antibiotics, were isolated from *Streptomyces hygroscopicus* AM-3672 and acknowledged as herbicidal agents[1]. The absolute configuration of herbimycin A was confirmed by X-ray crystallographic analysis[3]. The total synthesis of herbimycin A was reported by Tatsuta *et al*.[4] and Yu *et al*.[15](See Appendix-I).



Streptomyces hygrocopicus AM-3672



	R_1	R_2
Herbimycin A[2,3]	OCH_3	OCH_3
B[2,5,6]	OH	H
C[7]	OH	OCH_3

2. Physical data (Herbimycin A)[1]

Colorless powder. $C_{30}H_{42}N_2O_9$; mol wt 574.30. Sol. in MeOH, EtOH, $CHCl_3$, EtOAc, DMSO, acetone, DMF, benzene. Insol. in H_2O, Et_2O, hexane.

3. Biological activities[1,5,8,9]

1) Herbicidal activity of herbimycin A[1,5]

	Test plant	Pre-emergence system (g/area) 100	50	25	12.5	Post-emergence system (g/area) 100	50	25
Monocotyledon	*Oryza sativa*	2	1	1	0	0	0	0
	Echinochola crus-galli	5	5	5	4			
	Digitaria adescendens	5	5	5	4	5	4	4
	Cyperus microiria	5	5	5	5	5	5	5
Dicotyledon	*Chenopodium ficifolium*	5	5	5	4	5	5	5
	Portulaca oleracea	5	5	5	4	4	4	3
	Galinsoga ciliata	5	5	5	4	4	3	2
	Rorippa atrovirens	5	5	4	4	5	4	3

2) Anti-tobacco mosaic virus activity[5]

Antibiotic	Concentration (ppm)	Inhibition (%)	Phytotoxicity
Herbimycin A	25.0	95	—
	12.5	90	—
	6.2	92	—
	3.1	85	—
Herbimycin B	25.0	100	—
	12.5	93	—
	6.2	88	—
	3.1	58	—
Glendanamicin	25.0	99	—
	12.5	98	—
	6.2	98	—
	3.1	80	—
Macbecin I	25.0	53	—

3) Inhibition of macromolecular synthesis in ts/NRK cells[8)]

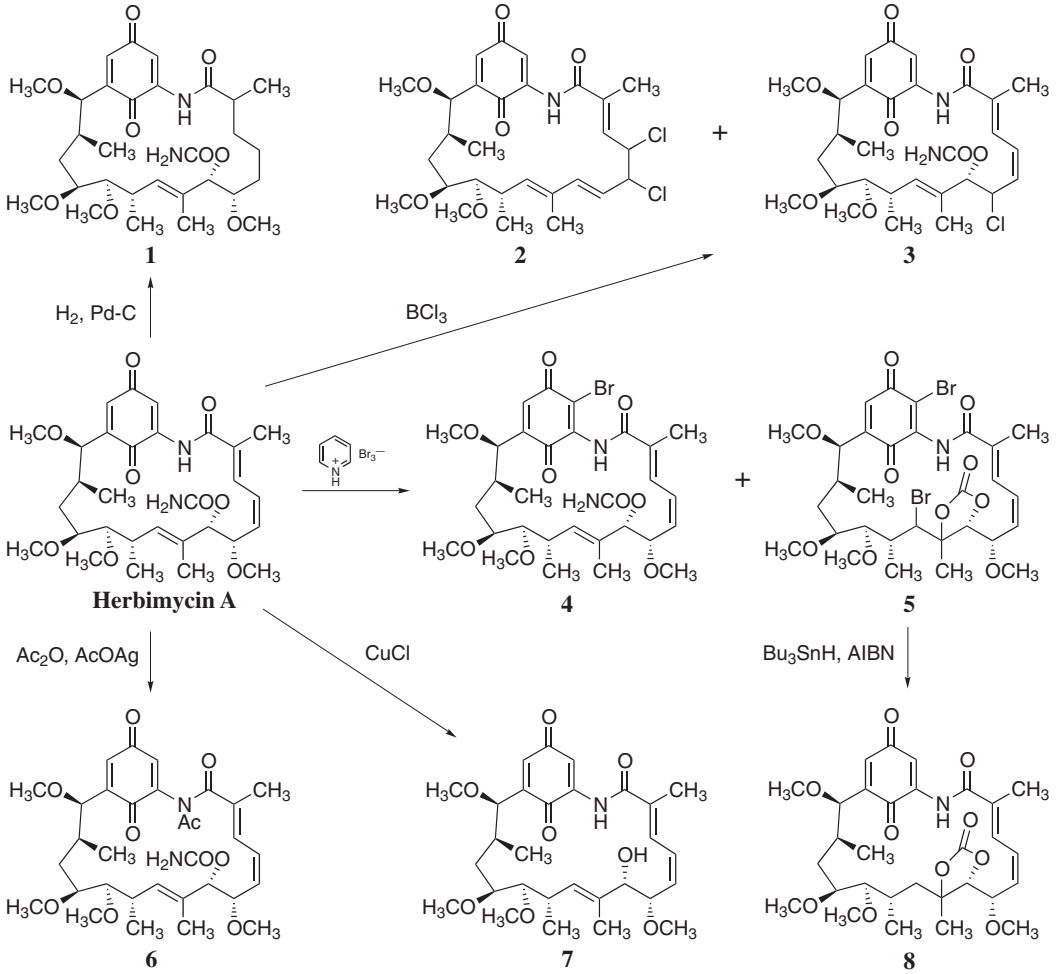
	Inhibition (%)
DNA	85.5
RNA	7.0
Protein	11.0

4) Effects on growth and differentiation of human erythroleukemia cells[9)]

	IC_{50} (ng/ml)	Hb
K562 cells	24.5	2.44
KU812 cells	19.1	1.63
HEL cells	141.7	1.23

5) Chemical modification and antitumor activity[10,11)]

Several halogenated and other related derivatives have been synthesized and evaluated *in vivo* for their activities against Ehrlich ascites carcinoma. Some of these derivatives showed higher *in vivo* activity than herbimycin A.



Antitumor activity of herbimycin A derivatives against Ehrlich ascites carcinoma

Compound	Total dose (mg/kg)	Dose (mg/kg x day)	T / C (%)	Number of* living/total
Herbimycin A	6.3	1.3 x 5	126	1/4
1	125	25.0 x 5	193	3/4
2	250	50.0 x 5	215	4/4
3	125	12.5 x 5	200	4/4
4	250	50.0 x 5	190	4/4
5	125	25.0 x 5	134	1/4
6	125	25.0 x 5	89	0/4
7	250	50.0 x 5	200	3/4
8	250	50.0 x 5	150	2/4

*Number of surviving mice at day 31.

6) Inhibition of tyrosine kinase activity[12)]
Since herbimycin A appears to exhibit specific inhibitory activity against tyrosine kinases in cells, this antibiotic is beneficial in determining whether tyrosine phosphorylation is involved in the mechanisms for cell transformation, growth, and differentiation.

7) Mechanism of antiproliferative and antitumor activity[13,14,16-21)]
Herbimysin A specifically inhibits the cytosolic chaperone HSP 90 and its endoplasmic reticulum (ER) homologue GRP 94. This compound has antiproliferative and antitumor effects: as it binds to HSP 90, it inhibits the HSP 90-mediated conformational maturation/refolding reaction, thereby promoting degradation of HSP 90 substrates, such as bcr-abl, mutant Flt3 and proteins of tumor angiogenic, apoptosis or ER stress signal transduction pathways[16-21)].

4. Biosynthesis[22)]
The biosynthetic gene cluster for herbimycin was identified and the biosynthetic pathway was proposed. It is synthesized from a 3-amino-5-hydroxybenzoic acid starter unit, followed by polyketide synthase processing and tailoring enzyme reactions.

5. References

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