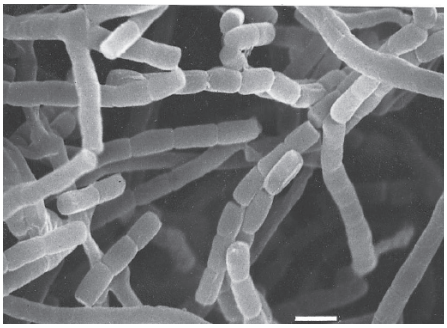
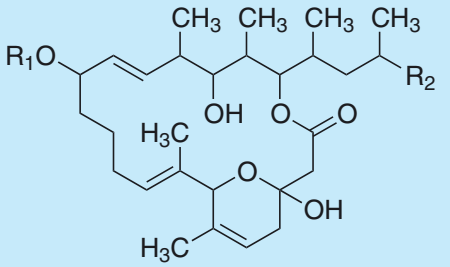
Irumamycin

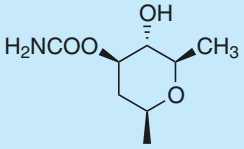
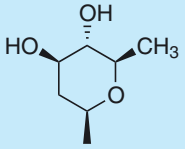
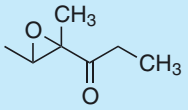
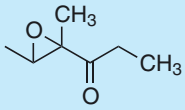
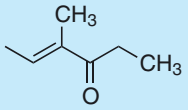
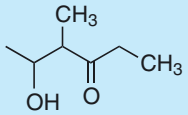
1. Discovery, producing organism and structures[1-4)]

Antifungal screening led to the discovery of the irumamycins from a culture broth of *Streptomyces subflavus*. *Subsequently,* a blocked mutant of the strain AM-3603^T was found to accumulate two lactones, named irumanolides I and II.



Streptomyces subflavus subsp. *irumaensis* AM-3603^T



	Irumamycin	3'-O-Decarbamoyl-irumamycin	Irumanolide I	Irumanolide II
R_1			H	H
R_2				

2. Physical data (Irumamycin)

White amorphous powder. $C_{41}H_{65}NO_{12}$; mol wt 763.45. Sol. in MeOH, EtOH, acetone. Insol. in H_2O, hexane, petroleum ether.

3. Biological activity[5)]

1) Antifungal activity

Test organism		MIC (μg/ml)*[1]					
		Iruma-mycin	Venturi-cidin A[6)]	Botry-cidin	Aabo-mycin A	Blasti-cidin S	Prumycin
Pyricularia oryzae	A*[2]	0.05	>0.03	0.05	<0.2	>100	>100
	B	>0.03	>0.03	0.03	<0.2	25	100
Sclerotinia cinerea	A	0.05	0.78	0.4	0.2	50	1.56
	B	0.1	0.78	0.78	0.2	25	6.25
Rhizoctonia solani	A	0.4	1.56	12.5	>100	>100	>100
	B	25	>25	>25	>100	>100	>100
Botrytis cinerea	A	—*[3]	—	—	>100	50	>100
	B	6.25	>25	12.5	>100	100	50
Alternaria kikuchiana	A	50	—	—	>100	50	>100
	B	12.5	5	12.5	100	12.5	50

*1 Glucose-potato agar, 2–3 days.
*2 A, isolated from an infected plant; B, laboratory stock culture.
*3 —, Not tested.

2) Protective effect against plant-pathogenic fungi

Protection of plants from fungal infection by irumamycin in pot tests

Pathogenic organism	Plant infected	Irumamycin (ppm)	Protection value (%)
Botrytis cinerea	Cucumber	200	98
		100	97
		50	97
Colletotrichum lagenarium	Cucumber	200	100
		100	99
		50	92
Cochliobolus miyabeanus	Rice plant	200	92

Calculated from an equation:

$$\left(1 - \frac{\text{No. of infectious lesions on treated plants}}{\text{No. of infectious lesions on control plants}}\right) \times 100$$

3) Antitrypanosomal activities[8)]

In the course of our screening program to discover new antitrypanosomal antibiotics, by screening metabolites from soil microorganisms, we have discovered 10 compounds that display potent antitrypanosomal activity *in vitro*. We reported the results of sensitivity tests on the GUTat 3.1 strain of *T. b. brucei* and the STIB900 strain of *T. b. rhodesiense* using the four commonly used antitrypanosomal drugs as well as detailing the novel antitrypanosomal activity and cytotoxicity of the ten antibiotics *in vitro*.

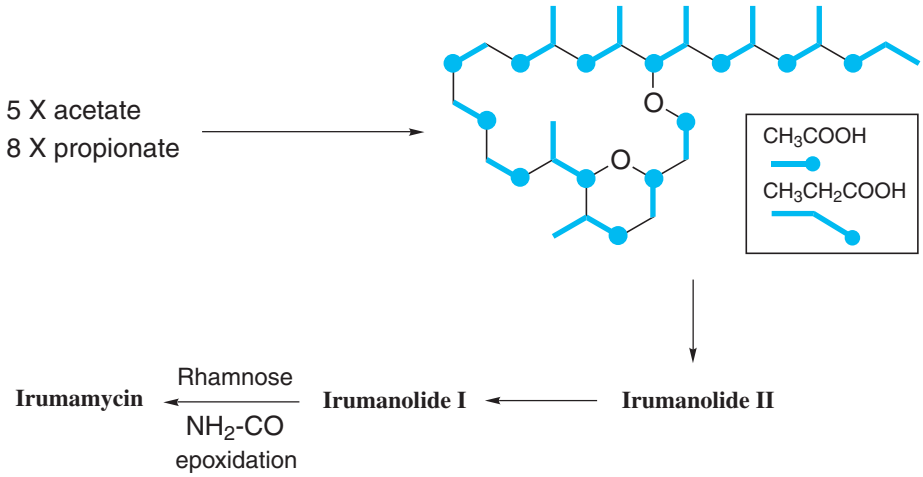
In vitro antitrypanosomal activity and cytotoxicity of 10 microbial metabolites

Compound	IC_{50} (ng/mL)				
	Antitrypanosomal activity		Cytotoxicity MRC-5	Selective index	
	GUTat 3.1	STIB900		MRC-5/ GUTat 3.1	MRC-5/STIB900
Aureothin	1.4	1.1	>25,000	>17,857	>22,727
Cellocidin	150	30	5,910	39	179
Destomycin A	330	210	21,140	64	101
Echinomycin	20	14	6,310	316	451
Hedamycin	14	18	>25,000	>1,786	>1,389
Irumamycin	20	31	>12,500	>625	>403
LL-Z 1272b	49	59	13,620	278	231
O-methylnanaomycin A	210	16	4,890	23	306
Venturicidin A	120	540	>25,000	>208	>185
Virustomycin A	0.45	480	80	178	0.2

GUTat 3.1: *Trypanosoma brucei brucei* strain
STIB900: *Trypanosoma brucei rhodesiense* strain
MRC-5: Human lung fibroblast cell line

4. Biosynthesis[4,7)]

The carbon skeleton of the aglycone moiety originated from 5 acetate and 8 propionate units. The biosynthetic pathway to irumamycin was proposed as shown below:



5. References

1. [228] S. Ōmura *et al*., *J. Antibiot*. **35**, 256-257 (1982)
2. [257] S. Ōmura *et al*., *J. Org. Chem*. **47**, 5413-5415 (1982)
3. [329] A. Nakagawa *et al*., *J. Antibiot*. **38**, 1266-1269 (1985)
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5. [302] S. Ōmura *et al*., *J. Antibiot*. **37**, 1572-1578 (1984)
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