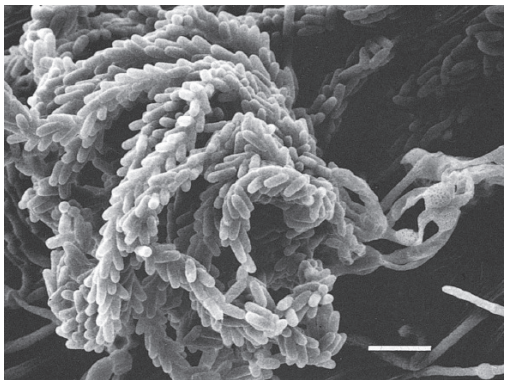
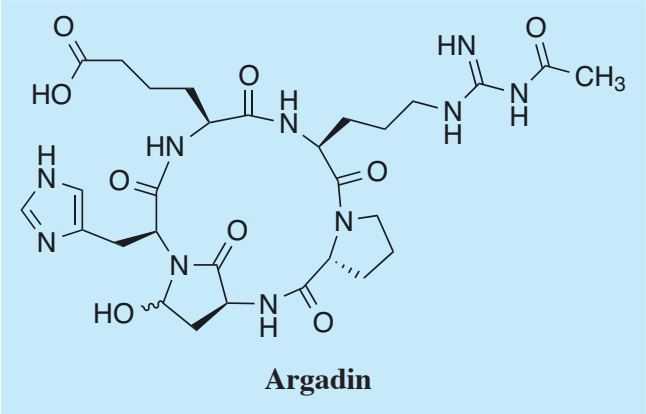
Argadin

1. Discovery, producing organism and structure[1,2,7-9)]

Argadin was isolated from the culture broth of fungal strain *Clonostachys* FO-7314 and identified as a chitinase inhibitor. It is a cyclic pentapeptide composed of N^{ω}-acetyl-L-arginine, D-proline, L-aspartic β-semialdehyde, L-histidine, and L-2-aminoadipic acid in which the aldehyde carbon of aspartic β-semialdehyde is bonded to the histidyl α-amino residue. The stereochemistry of C_{α} and C_{γ} of aspartic β-semialdehyde and C_{α} of histidine were elucidated from the crystal structure of the argadin-chitinase complex. Argadin is the first peptide inhibitor of glycosidase showing nanomolar inhibition, and the argadin-chitinase complex revealed how the argadin backbone and side chains mimic the interactions of the enzyme with chitooligosaccharides. The first total synthesis of argadin was reported by Eggleston *et al*.[3)], and it is shown to exist as a 5:1 mixture of diastereoisomers at C_{γ} of aspartic β-semialdehyde.



Clonostachys sp. FO-7314
Bar: 10 μm



Argadin

2. Physical data

White powder. $C_{29}H_{42}N_{10}O_9$; mol wt 674.72. Sol. in acidic H_2O, acidic DMSO. Slightly sol. in H_2O, DMSO. Insol. in MeOH, acetone, $CHCl_3$.

3. Biological activity

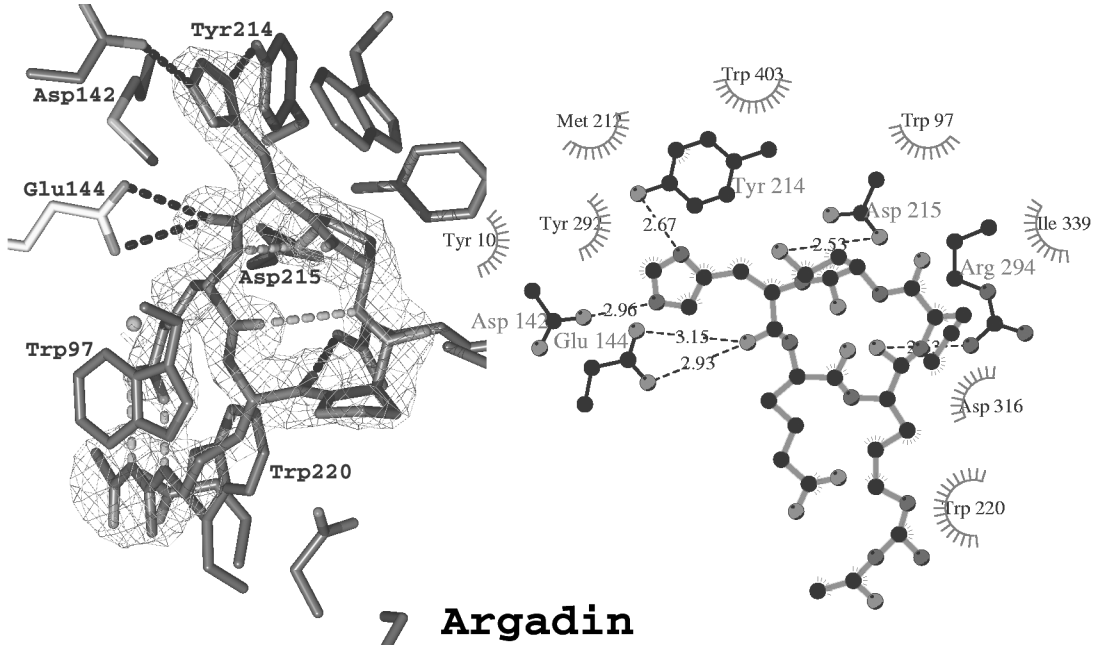
1) Chitinase inhibition[1,2)]

		IC_{50} (μM)[a]			
	Temperature	Argadin	Argifin[b]	Riboflavin[c]	Allosamidin[d]
Lucilia cuprina chitinase[e]	20°C	0.0034	0.103	N.T.	0.0004
Lucilia cuprina chitinase[e]	37°C	0.15	3.7	2.1	0.0023
Streptomyces griseus chitinase	37°C	1.9	14.8	>200	0.016
Bacillus subtilis chitinase	37°C	1.9	19.0	>200	0.025
Serratia marcescens chitinase B[a]	37°C	0.0192	32.5	N.T.	0.45

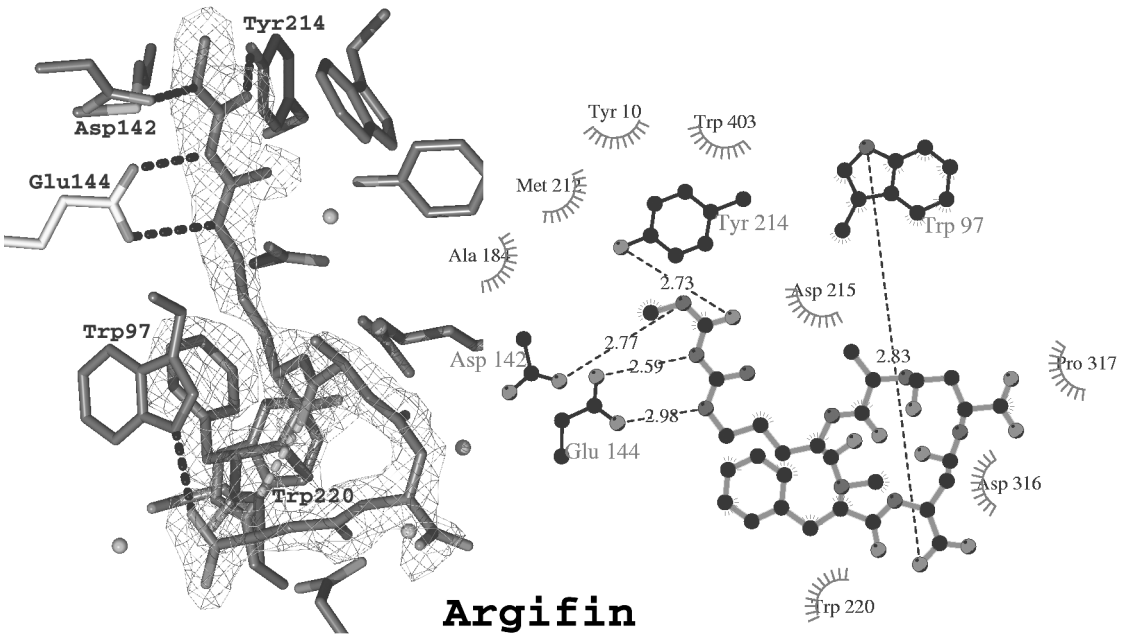
[a] *S. marcescens* chitinase inhibition data are reported as K*i* values.
[b] Argifin is a new compound isolated in Kitasato (see Argifin).
[c] Riboflavin was isolated from a *Penicillium* strain as a chitinase inhibitor in Kitasato[4)].
[d] Allosamidin is a representative chitinase inhibitor.
[e] *Lucilia cuprina* is sheep blowfly.

2) Argadin-chitinase complex and argifin-chitinase complex[2,5,6,10)]

The structures of argifin and argadin in complex with *Serratia marcescens* chitinase B were resolved (2.0 Å resolution). These structures give an unprecedented view of how peptide based inhibitors inactivate carbohydrate-processing enzyme. For example, the carbonyl oxygen of the histidine in argadin occupies almost the same position as the scissile oxygen in the chitinase B-chitooligosaccharide complex and hydrogen-bonds to the catalytic acid (Glu144), while Glu-144 makes hydrogen bonds to the guanidinium group of the arginine side chain in argifin. The structures of argifin and argadin in complex with *Aspergillus fumigatus* chitinase and human bacterial-class chitinase (chitotriosidase) were also resolved[5)].



7 Argadin



Argifin

3) Insecticidal activity[1)]

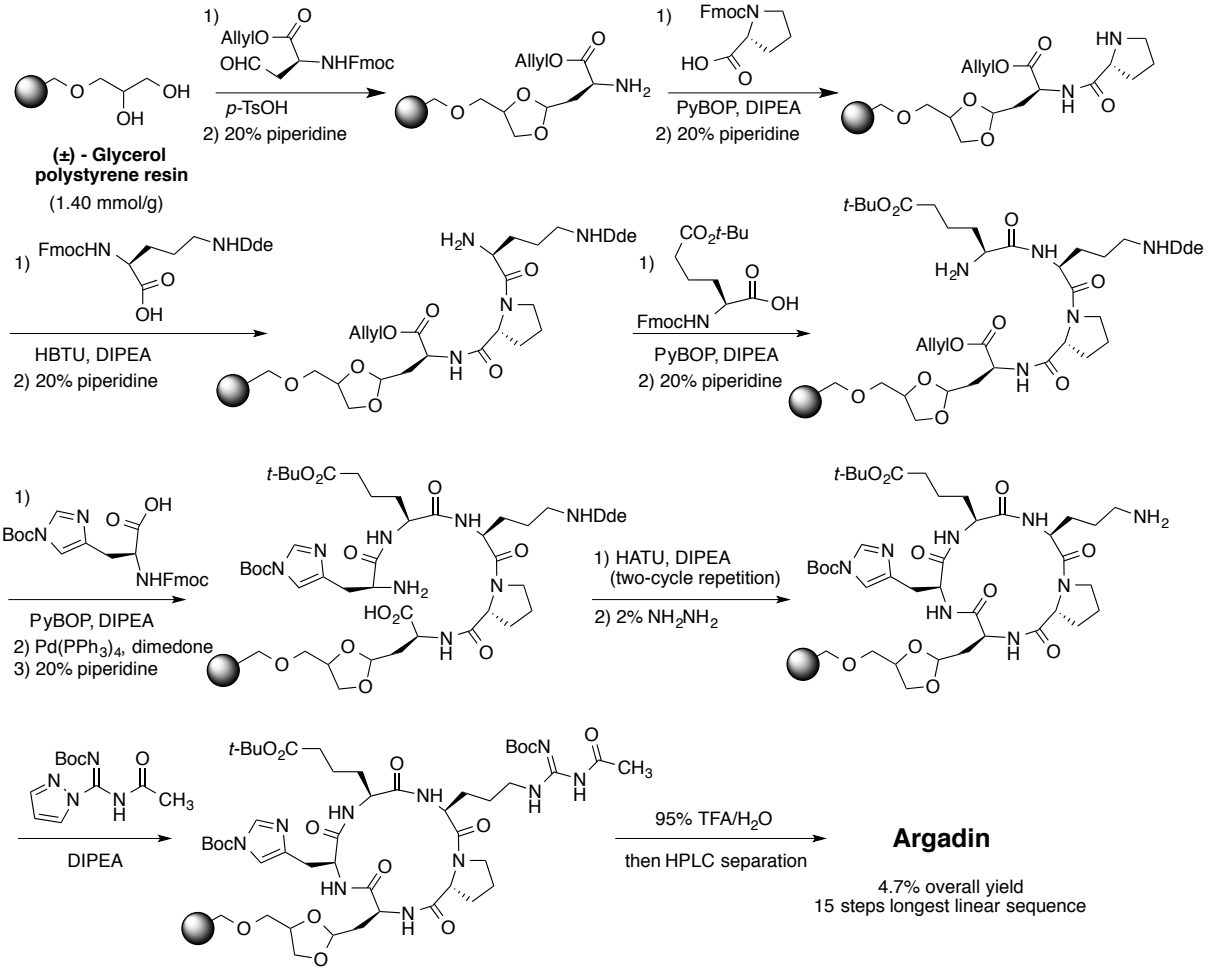
Argadin was injected into American cockroach (*Periplaneta americana*) larvae and compared with mock injected controls. No mortality was observed for control cases after day 1, while 60% and 38% mortality was observed for cockroaches injected with 20 μg and 2 μg of argadin, respectively.

4) Other biological activity[1)]

Argadin did not inhibit the growth of tested bacteria, yeast, or fungi at 10 μg/disc (paper disc method). Argadin also did not inhibit the growth of P388, KB, or HL-60 cells at 25 μg/ml.

4. Total synthesis[3,11)]

The total synthesis of argadin was reported by two groups[3,11)]. Below is a scheme achieved by Ōmura *et al*.[11)] (See Appendix-I).



5. References

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