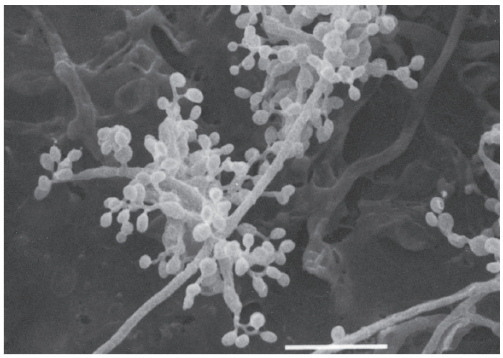
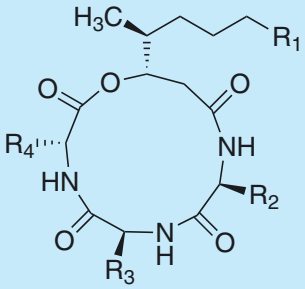
Beauveriolide

1. Discovery, producing organism and structures [1-5,10)]

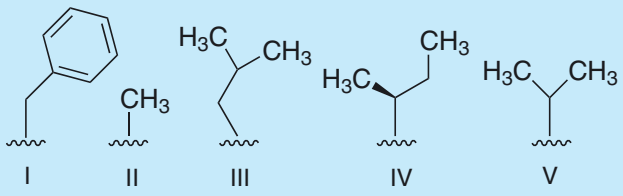
Beauveriolides I[1-3)], III[2,3)], IV, V, VI, VII, VIII and IX[5)] (beauveroplide Fa[4)]) were isolated from the culture broth of the fungal strain *Beauveria* sp. FO-6979 and identified by means of an intact cell assay as inhibitors of macrophage foam cell formation. Beauveriolides have a cyclodepsipeptide structure consisting of three amino acids and a ß-hydroxylic acid. Beauveriolide I has been reported as an insecticidal agent [1)], beauveriolide IX was identified as beauveriolide Fa[4)], and the planar structure of beauveriolide VI was identical with that of beauveriolide M[5)].



Beauveria sp. FO-6979
Bar: 10 μm



Beauveriolides	R_1	R_2	R_3	R_4
I	$-CH_3$	I	II	III
III	$-CH_3$	I	II	IV
IV	$-CH_3$	V	II	V
V	$-CH_3$	V	II	IV
VI	$-CH_3$	V	II	III
VII	$-CH_3$	I	II	V
VIII	$-(CH_2)_2CH_3$	V	II	IV
IX	$-CH_3$	I	I	IV



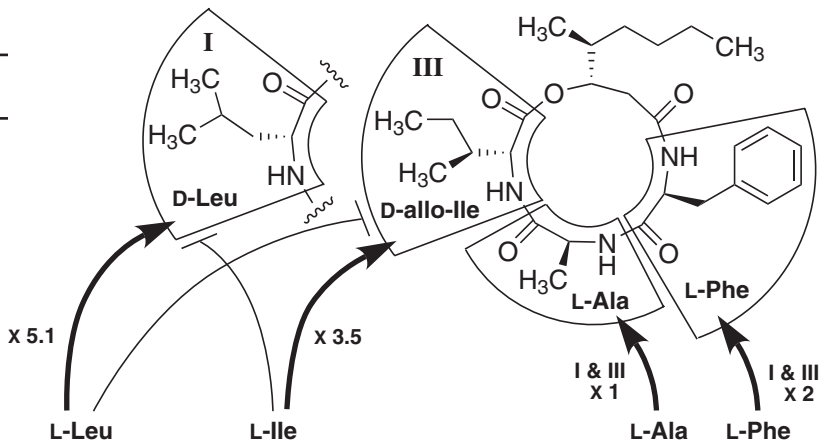
2. Physical data (Beauveriolide III)[3)]

White powder. $C_{27}H_{41}N_3O_5$; mol wt 487.30. Sol. in MeOH, EtOH, acetone, CH_3CN, EtOAc, $CHCl_3$. Insol. in H_2O, hexane.

3. Fermentation[6)]

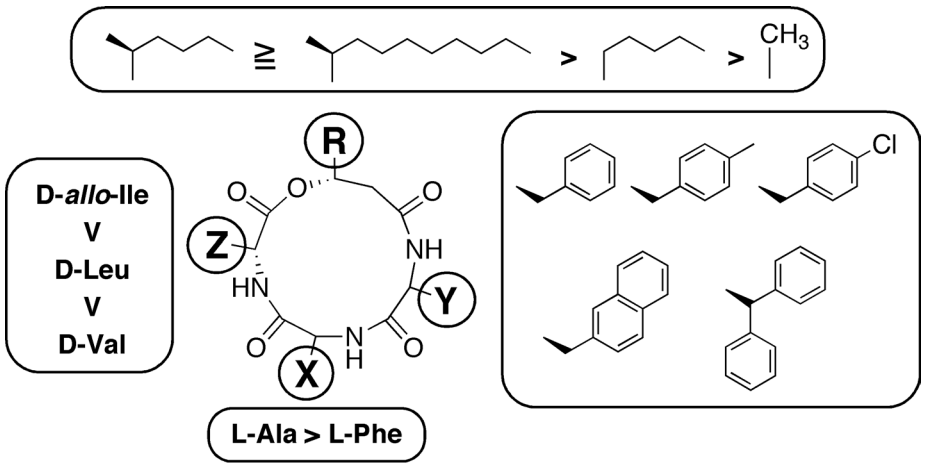
Addition of L-Leu or L-Ile, but not D-Leu or D-allo-Ile, to the culture medium yielded high and selective production of beuveriolide I or III.

Condition	Production (μg/mL)	
	Beauveriolide I	III
Control	25.0	50.0
+ L-Ile	5.6	172.0
+ D-Ile	25.0	50.0
+ L-*allo*-Ile	24.0	42.0
+ D-*allo*-Ile	14.0	33.0
+ L-Leu	127.0	26.0
+ D-Leu	24.0	48.0
+ L-Phe	66.0	79.0
+ L-Ala	15.4	26.6
+ L-Val	6.8	7.9



4. Structure-activity relationship[8,9,11)]

Comparison of ACAT inhibitory activity among natural beauveriolides and synthetic derivatives[8,9,10)] revealed the structure-activity relationship.

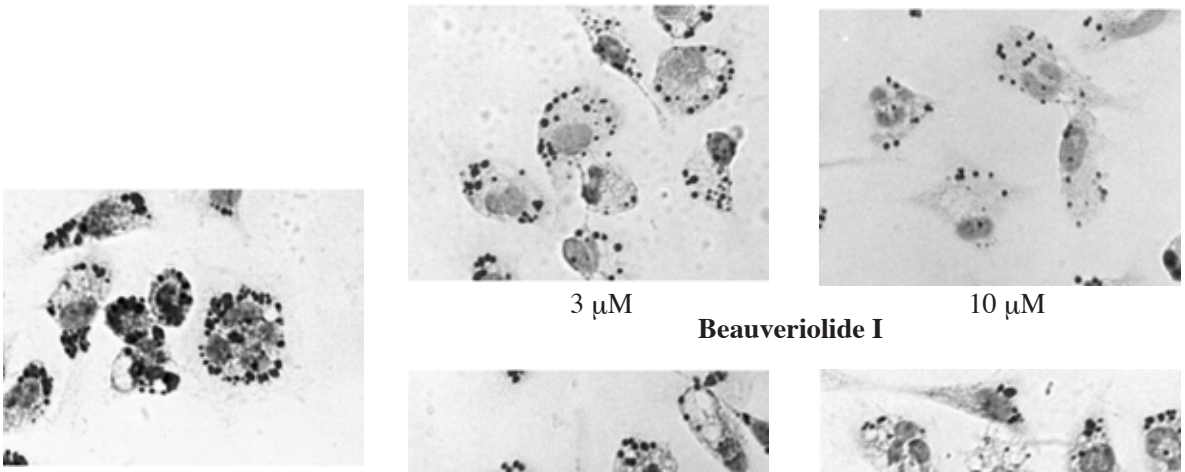


5. Biological activity[2,12-14)]

Inhibition of lipid droplet formation in mouse peritoneal macrophages.

In the early stages of atherosclerogenesis, macrophages that penetrate into the intima accumulate massive lipid droplets in the cytosols, and are converted into foam cells, leading to the development of atherosclerosis in the arterial wall. Therefore, inhibitors of macrophage lipid droplet formation would be expected to retard progression of atherosclerosis.

Inhibitory activity against lipid droplet formation in macrophages was tested in a cell assay using mouse peritoneal macrophages. Beauveriolides I and III led to a reduction in the number and size of cytosolic lipid droplets in macrophages at 15 μM without any cytotoxic effect on the macrophages.



Control

3 μM

10 μM

Beauveriolide I

3 μM

10 μM

Beauveriolide III

6. References

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