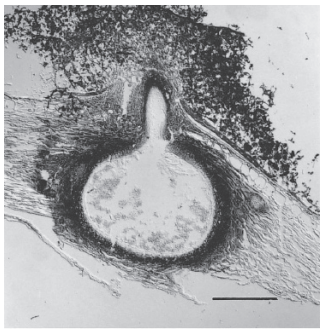
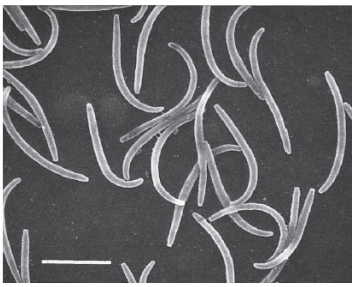
Phenochalasin

1. Discovery, producing organism and structures[1,2)]

Phenochalasins A and B were isolated from the culture broth of *Phomopsis* fungal strain FT-0211[1, 2)] and recognized based on a cell-based assay, to be inhibitors of macrophage foam cell formation. Although phenochalasins belong to the cytochalasan family, phenochalsin A has the only cytochalasan skeleton containing a phenyl moiety.

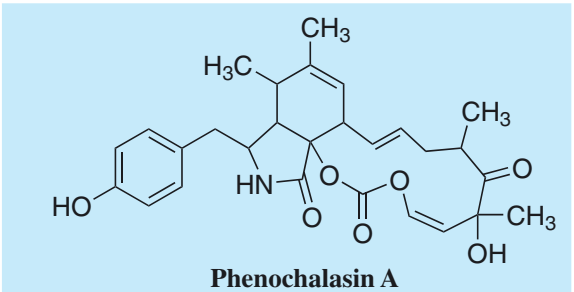


Conidioma, Bar: 200 μm

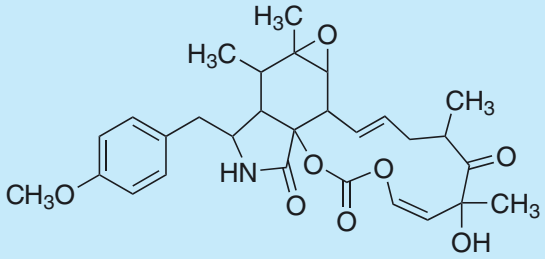


Conidia, Bar: 10 μm

Phomopsis sp. FT-0211



Phenochalasin A



Phenochalasin B

2. Physical data (Phenochalasin A)[1)]

White powder. $C_{28}H_{33}NO_7$; mol wt 495.23; Sol. in MeOH, EtOH, acetone, CH_3CN, EtOAc, $CHCl_3$. Insol. in H_2O, hexane.

3. Biological activity[1,3,4)]

1) Inhibition of lipid droplet formation in mouse peritoneal macrophages[1,3)].

Inhibitory activity against lipid droplet formation in macrophages (See also “Beauveriolide” (p. 64)) by cytochalasans was tested in a cell assay using mouse peritoneal macrophages. Phenochalasin A inhibited lipid droplet formation in a dose-dependent manner up to 20 μM without morphological changes in the macrophages. The other cytochalasans inhibited lipid droplet formation over a narrow concentration range and morphological changes in macrophages were observed.

2) Inhibition of neutral lipid synthesis in macrophages[1,3].
Inhibitory activity against neutral lipid synthesis (cholesteryl ester (CE) and triacylglycerol (TG)) in the cytosolic lipid droplet was tested. Phenochalasin A and cytochalasins D and E inhibited CE synthesis, while the other cytochalasans inhibited both CE and TG synthesis.

Effects of cytochalasans on cholesteryl ester and triacylglycerol synthesis, morphology and toxicity in mouse macrophages.

Compound	IC_{50}[a]		Morphology[b]	Cytotoxicity[c]	Cytotoxicity / IC_{50} of CE
	CE	TG			
Phenochalasin A	0.61	>19	>19	>20	>32.8
Phenochalasin B	0.2	0.38	0.18	0.5	2.2
Cytochalasin B	2.9	11.4	1.8	10	3.4
Cytochalasin D	2.4	>19	1.8	>20	>8.3
Cytochalasin E	0.20	>19	0.19	2.0	10
Aspochalasin F	3.0	5.0	2.3	2.0	0.67
Aspochalasin G	1.0	2.0	2.4	1.0	1.0

a: Concentration of a compound which inhibits [^{14}C]CE or [^{14}C]TG synthesis from [^{14}C]oleic acid by 50% in macrophages.
b: Minimal concentration of a compound which shows morphological changes in macrophages.
c: Concentration of a compound which causes 50% viability of macrophages in a MTT assay.

Phenochalasin A showed no activity against ACAT1 and ACAT2 as compared with the IC_{50} values of CE synthesis (0.6 μM) in the macrophage assay, indicating that their molecular targets in macrophage are not ACAT.[4]

4. References

1. [728] H. Tomoda *et al., J. Antibiot.* **52**, 851-856 (1999)
2. [729] H. Tomoda *et al., J. Antibiot.* **52**, 857-861 (1999)
3. [740] I. Namatame *et al., J. Antibiot.* **53**, 19-25 (2000)
4. [955] T. Ohshiro *et al., J. Antibiot.* **60**, 43-51 (2007)