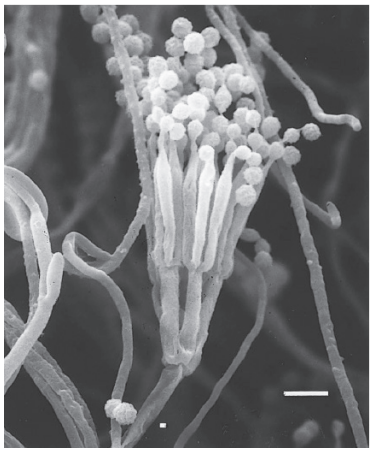
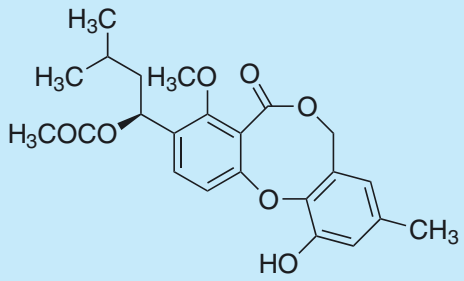
Purpactin

1. Discovery, producing organism and structure[1,2,6)]

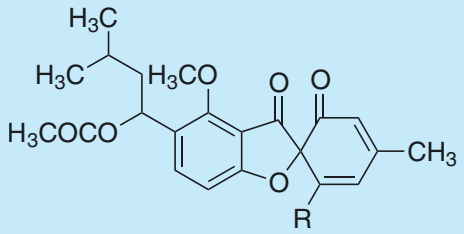
Purpactins were isolated from the culture broth of *Penicillium purpurogenum* (current name: *Talaromyces purpurogenus*[6)]) FO-608 and found to be inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT) from an assay using rat liver microsomes an enzyme source.



Penicillium purpurogenum FO-608
(*Talaromyces purpurogenus* FO-608)
Bar: 5 μm



Purpactin A



Purpactin B R = CH_2OH
C R = CHO

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

Colorless powder. $C_{23}H_{26}O_7$; mol wt 414.17. Sol. in MeOH, $CHCl_3$. Insol. in hexane, H_2O.

3. Biological activity[1,7)]

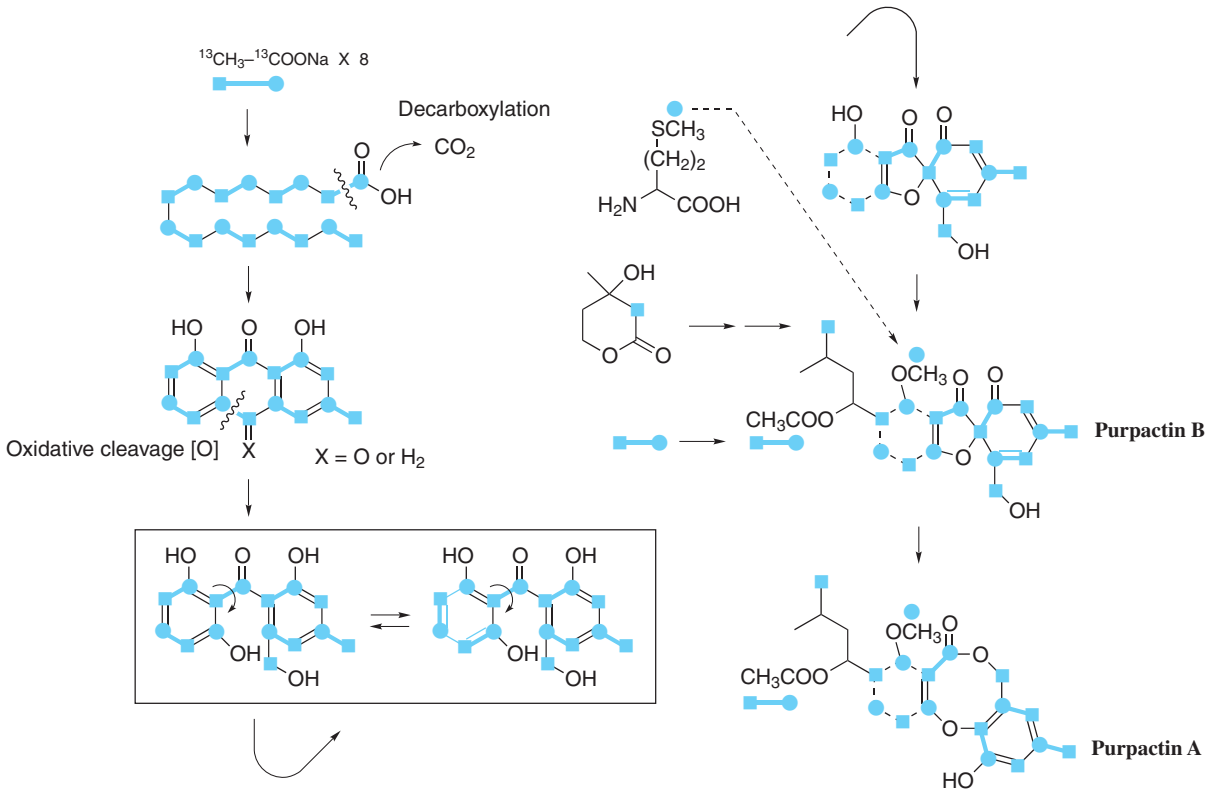
ACAT play an important role in three events that contribute to the atherosclerotic process; absorption of dietary cholesterol from the intestines, lipoprotein synthesis in the liver and accumulation of cholesteryl esters as oil droplets in macrophages and smooth muscle cells of developing arterial lesions. Therefore, ACAT inhibitors are expected to retard progression of atherosclerosis. ACAT inhibitory activity was tested in an enzyme assay using rat liver microsomes and in a cell assay using J774 macrophages. Cytotoxicity (CD_{50}) was also determined by the cell assay. Purpactins are as the first microbial ACAT inhibitors discovered.

Compound	Rat liver microsomes	J774 macrophages	
	IC_{50} (μM)	IC_{50} (μM)	CD_{50} (μM)
Purpactin A	121	1.2	9.7
Purpactin B	126	NT	NT
Purpactin C	126	NT	NT

Purpactin A inhibited ACAT1 (IC_{50}= 2.5 μM) and ACAT2 (IC_{50}= 1.5 μM,) to similar extent.[7)]

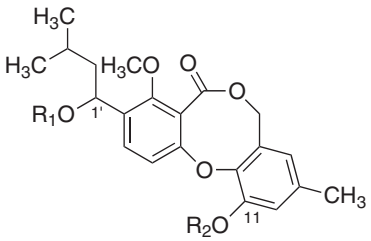
4. Biosynthesis[2,3)]

Purpactin B is the first isogrisan compound derived from a single octaketide chain. It is nonenzymatically converted to purpactin A in accordance with the following scheme[2)].



5. Chemical modification[4)]

Acylated derivatives were prepared from deacetylated purpactin (penicillide)[5)] and their ACAT inhibitory activity was tested.



Derivative	R1 (C-1')	R2 (C-11)	Rat (liver) microsomes IC_{50} (μM)	J774 macrophages IC_{50} (μM)	J774 macrophages CD_{50} (μM)	J774 macrophages CD_{50}/IC_{50}
1 [a)]	CH_3CO	H	120	1.2	9.7	8.1
2 [b)]	H	H	>269	>26.9	>26.9	–
3	CH_3CO	THP [c)]	84	5.0	>25.1	>8.4
4	H	THP [c)]	182	28.5	>28.5	>1.0
5	$CH_3(CH_2)_{14}CO$	H	>164	>16.4	>16.4	–
6	$CH_3(CH_2)_2CO$	H	60	1.4	9.3	6.6
7	CH_3CO	$CH_3(CH_2)_{14}CO$	>153	>15.3	>15.3	–
8	CH_3CO	$CH_3(CH_2)_2CO$	81	2.5	>20.7	>8.3
9	H	$CH_3(CH_2)_{14}CO$	>164	>16.4	>16.4	–
10	$CH_3(CH_2)_{14}CO$	$CH_3(CH_2)_{14}CO$	>118	>11.8	>11.8	–
11	H	$CH_3(CH_2)_2CO$	60	>30.1	11.6	<2.6
12	$CH_3(CH_2)_2CO$	$CH_3(CH_2)_2CO$	88	>19.6	19.6	<1.0
13	CH_3CO	CH_3	224	11.7	9.3	0.8

a) Purpactin A b) Penicillide c) Tetrahydropyranyl

6. References

1. [457] H. Tomoda *et al.*, *J. Antibiot.* **44**, 136-143 (1991)
2. [458] H. Nishida *et al.*, *J. Antibiot.* **44**, 144-151 (1991)
3. [477] H. Nishida *et al.*, *J. Org. Chem.* **57**, 1271-1274 (1992)
4. [459] H. Nishida *et al.*, *J. Antibiot.* **44**, 152-159 (1991)
5. T. Sassa *et al.*, *Tetrahedron Lett.* **45**, 3941-3942 (1974)
6. R. A. Samson *et al. Stud. Mycol.* **70**, 159-183 (2011)
7. [955] T. Ohshiro *et al., J. Antibiot.* **60**, 43-51 (2007)