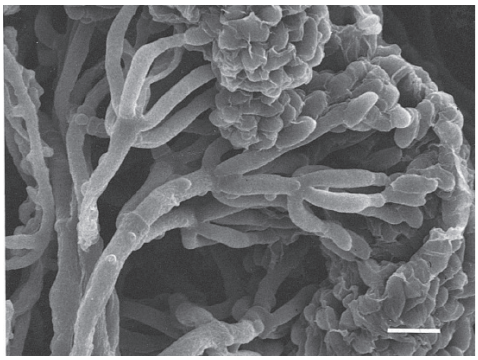
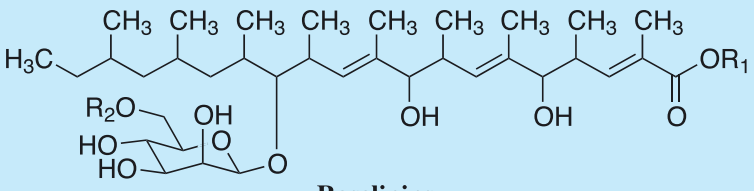
Roselipin

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

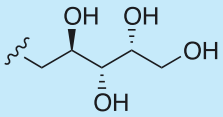
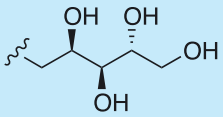
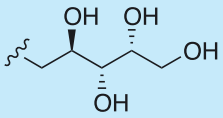
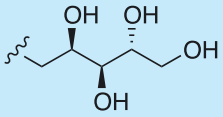
Roselipins were isolated from the culture broth of *Gliocladium roseum* stain KF-1040 and recognized to be inhibitors of diacylglycerol acyltransferase (DGAT). Four active compounds, designated roselipins 1A, 1B, 2A and 2B were isolated. Roselipins A and B are stereoisomers of D-arabinitol.



Gliocladium roseum KF-1040
Bar: 5 μm



Roselipins

	R_1	R_2
Roselipin 1A		H
Roselipin 1B		H
Roselipin 2A		$COCH_3$
Roselipin 2B		$COCH_3$

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

White power. $C_{40}H_{72}O_{14}$; mol wt 776.49. Sol. in MeOH, $CHCl_3$, CH_3CN, acetone, EtOH, EtOAc. Insol in. H_2O, hexane.

3. Biological activity[1,3-7)]

1) DGAT inhibitory activity[1,3,4)]

DGAT is involved in triacylglycerol formation. Therefore, DGAT is considered a new target for treatmenting diseases caused by TG accumlation including; obesity, fatty liver and hypertriglyceridemia [See Amidepsine (p. 68)]. Roselipins inhibit DGAT activity in rat microsomes with similar IC_{50} values.

Demanosyl and/or dearabinitoyl roselipins were prepared chemically and enzymatically. Demanosyl roselipins conserved DGAT inhibitory activity, while others lost activity, indicating that the arabinitoyl fatty acid core is essential for eliciting activity.

DGAT inhibitory activity of roselipin derivatives R-3A, R-3B, R-4 and R-5

Compound		IC_{50} (μM)	
		Enzyme assay	Cell assay
Roselipin	1A	17	39
	1B	15	32
	2A	22	24
	2B	18	18
Derivative	R-3A	60	11
	R-3B	33	10
	R-4	> 760	200
	R-5	> 960	250

Roselipins are selective inhibitors of DGAT2. Roselipins 1A, 1B, 2A, and 2B inhibited DGAT2 with IC_{50} values of 30-50 μM, however showed almost no inhibition against DGAT1 even at 200 μM.[5)]

2) HIV integrase inhibitory activity[6)]
Roselipins 2A and 2B mixture showed HIV integrase inhibitory activity with IC_{50} of 8.5 μM.

3) Inhibitory activity of chemokine receptor CXCR3 interaction[7)]
Roselipins blocked chemokine receptor CXCR3 interaction of IP-10 ligand. Roselipins 2A, 2B and 1A showed IC_{50} values of 14.6, 23.5, and 41 μM, respectively.

4. References

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3. [786] H. Tomoda and S. Ōmura, In *Enzyme Technology for Pharmaceutical and Biotechnological Applications*. (Eds Kirst, H., Yeh, W.-K. & Zmijewski, M.) pp.343-378, Marcel Dekker, Inc., New York. (2001)
4. [822] H. Tomoda *et al*., *J. Antibiot*. **56**, 24-29 (2003)
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