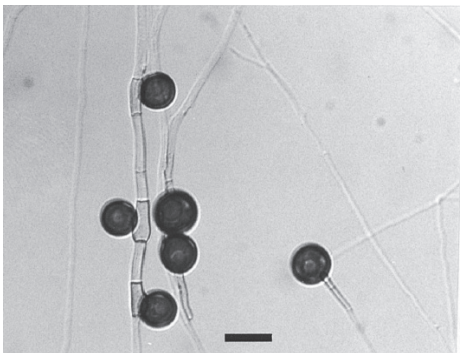
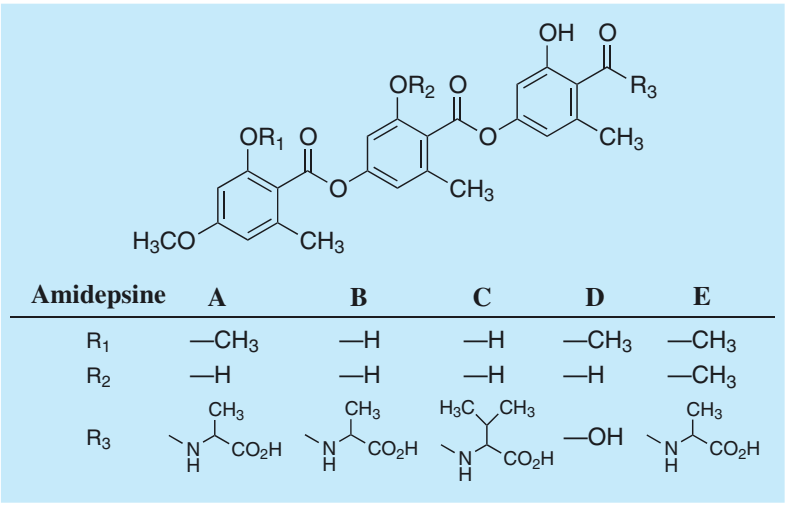
Amidepsine ©

1. Discovery, producing organism and structures[1-8)]

Fungal strains *Humicola grisea* FO-2942 and FO-5969 were found to produce a series of new inhibitors of diacylglycerol acyltransferase (DGAT). Five active compouds designated as amidepsines A, B, C, D and E were isolated. Amidepsine D is identical to 2,4-di-*O*-methylgyrophoric acid isolated from a lichen[4)]. The total synthesis of Amidepsine B was reported by Ōmura *et al*.[5)] (See Appendix-I).



Humicola sp. FO-5969
(*Humicola grisea* FO-5969)
Bar: 20 μm



Amidepsine	A	B	C	D	E
R_1	—CH_3	—H	—H	—CH_3	—CH_3
R_2	—H	—H	—H	—H	—CH_3
R_3				—OH	

2. Physical data (Amidepsine A)[2)]

Pale yellow powder. $C_{29}H_{29}O_{11}N$; mol wt 567. Sol. in MeOH, benzene, $CHCl_3$, EtOAc. Insol. in H_2O, hexane.

3. Biological activity[1)]

DGAT is exclusively involved in triacylglycerol formation. Excessive accumulation of triacylglycerol can cause fatty liver, obesity and hypertriglyceridemia, which lead to serious diseases such as atherosclerosis, diabetes and metabolic disorders. Therefore, DGAT is a target for pharmaceutical inhibition. The inhibitory acitivity of DGAT was tested by an enzyme assay using rat liver microsomes and by a cell assay using Raji cells. Amidepsines are the first known DGAT inhibitors.

Compound		IC_{50} (μM)	
		Rat liver microsomes	Raji cells
Amidepsine	A	10.2	15.5
	B	19.2	3.35
	C	51.6	17.2
	D	17.5	2.82
	E	124	NT

NT; not tested

4. References

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4. J. A. Elix *et al*., *Aust*. *J*. *Chem*. **34**, 1757-1761(1981)
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