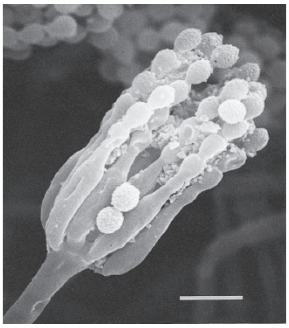
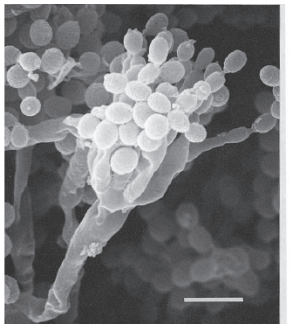
Isochromophilone

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

Isochromophilones I and II were isolated from the culture broth of *Penicillium multicolor* FO-2338[1,3,4)]. They were found to be novel gp120-CD4 binding inhibitors. Isochromophilones III–VI were isolated from the culture broth of *Penicillium* sp. FO-3216 and recognized as inhibitors of acyl-CoA: cholesterol acyltransferase (ACAT)[2)]. Isochromophilones VII and VIII were isolated from the culture broth of *Penicillium* sp. FO-4164[5)] and found to be inhibitors of both ACAT and diacylglycerol acyltransferse (DGAT). The structures of isochromophilones were elucidated by NMR analysis. Isochromophilones, members of the azaphilone family, have an oxoisochromane ring. Among this group, isochromophilone I is a complex of two isomers (**a** and **b**) which are easily converted from one isoform to another.

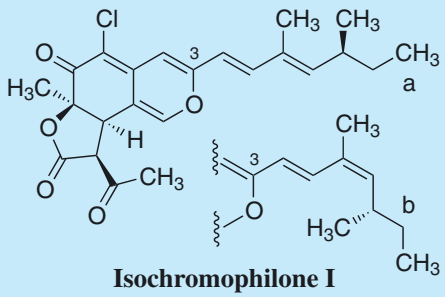


Penicillium multicolor FO-2338
Bar: 5 μm

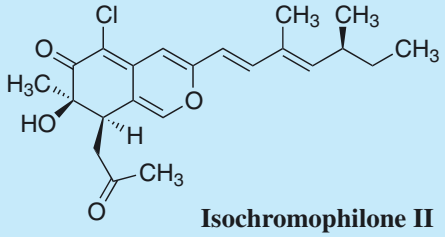


Penicillium sp. FO-3216
Bar: 5 μm

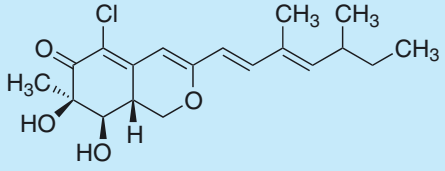
Penicillium sp. FO-4164
Bar: 5 μm



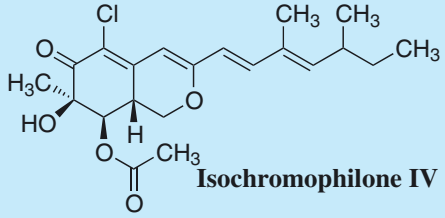
Isochromophilone I



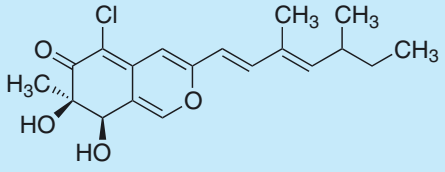
Isochromophilone II



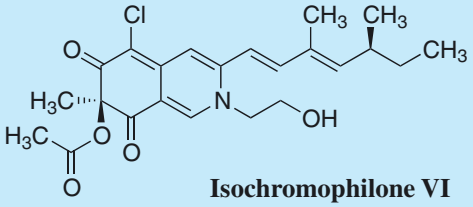
Isochromophilone III



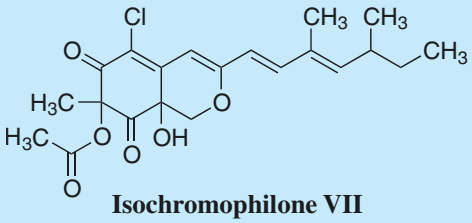
Isochromophilone IV



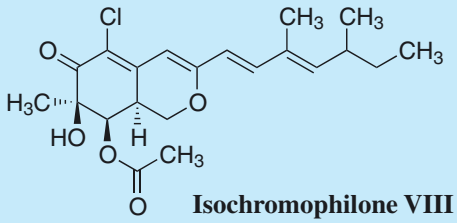
Isochromophilone V



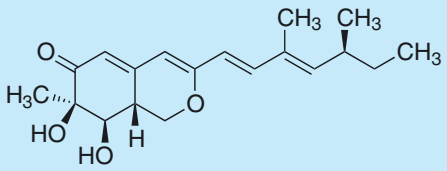
Isochromophilone VI



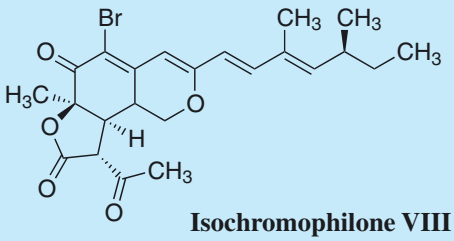
Isochromophilone VII



Isochromophilone VIII



Isochromophilone VII



Isochromophilone VIII

2. Physical data (Isochromophilone I)

Yellow powder. $C_{23}H_{25}O_5Cl$; mol wt 416.14. Sol. in acetone, $CHCl_3$, EtOH, MeOH, EtOAc. Insol. in hexane, H_2O.

3. Biological activity[1-3,5)]

1) Inhibition of gp120-CD4 binding[1,3)]

Compound	IC_{50} (μM)*
Isochromophilone I	6.6
Isochromophilone II	3.9

* Binding activity between recombinant soluble CD4 and recombinant gp120 was determined by ELISA.

2) Inhibition of HIV replication[1)]

Compound	Viral core protein p24 synthesized (ng/ml) Day 2	Day 3	Day 4
None	0	97.3	129.6
Isochromophilone II (10 μg/ml)	0	0	13.5

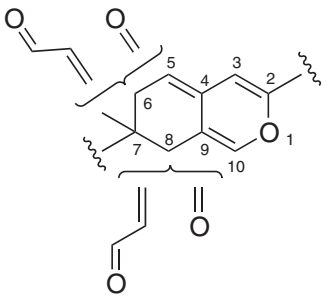
3) Inhibition of DGAT and ACAT activities[2,5)]

	IC_{50} (μM)	
Compound	DGAT	ACAT
IsochromophiloneIII	NT	110
IV	63.5	50.0
V	NT	50.0
VI	NT	120
VII	20.0	24.5
VIII	127	47.0

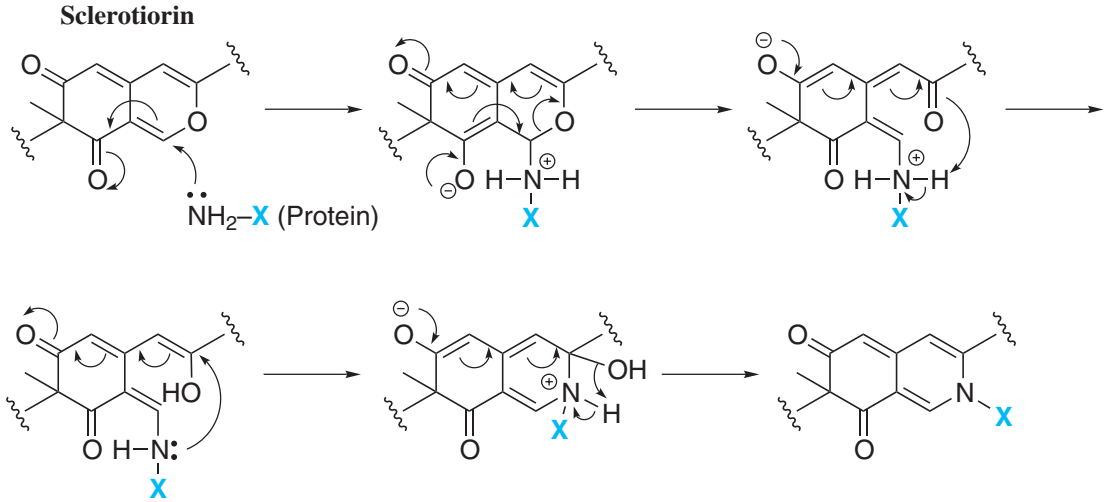
NT; not tested
DGAT and ACAT activities were analyzed by enzyme assays using rat liver microsomes as an enzyme source.

4) Inhibition of CETP activities by azaphilones[6)]

Certain members of the azaphilone family were found to inhibit CETP activity. Chaetoviridin B showed the most potent CETP inhibition with an IC_{50} value of < 6.2 μM, followed by sclerotiorin (IC_{50}; 19.4 μM) and deacetylsclerotiorin (IC_{50}; 19.4 μM). From the SAR, the common substructure shown below is essential for eliciting CETP inhibitory activity. Azaphilones are thought to react with primary amines in CETP to form adducts.



Common substructure of azaphilones essential for eliciting CETP inhibition



A possible reaction mechanism for formation of sclerotiorin adducts

4. References

1. [529] S. Ōmura *et al.*, *J. Antibiot.* **46**, 1908-1911 (1993)
2. [578] N. Arai *et al.*, *J. Antibiot.* **48**, 696-702 (1995)
3. [579] K. Matsuzaki *et al.*, *J. Antibiot.* **48**, 703-707 (1995)
4. [580] K. Matsuzaki *et al.*, *J. Antibiot.* **48**, 708-713 (1995)
5. [607] D. J. Yang *et al.*, *J. Antibiot.* **49**, 223-229 (1996)
6. [714] H. Tomoda *et al.*, *J. Antibiot.* **52**, 160-170 (1999)
7. [705] K. Matsuzaki *et al.*, *J. Antibiot.* **51**, 1004-1011 (1998)