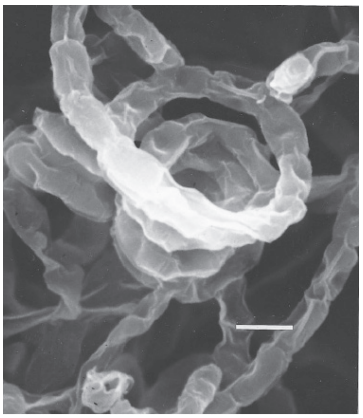
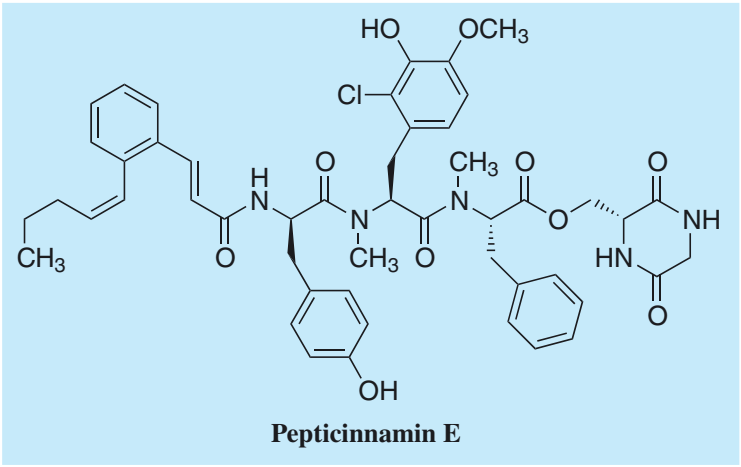
Pepticinnamin

1. Discovery, producing organism and structure[1-3)]

Pepticinnamins, consisting of 6 components, were isolated from the culture broth of the actinomycete strain OH-4652 and recognized as inhibitors of protein farnesyltransferase from an assay using a partially purified enzyme from human monocyte THP-1 (ATCC TIB 202). The structure of component E was elucidated. The Stereochemistry of the amino acids was elucidated using chiral HPLC, with the exception of *N*-methyl-(2-chloro-3-hydroxy-4-methoxy)-phenylalanine. Its stereochemistry was revealed by total synthesis of the pepticinnamin E diastereomers[3)] (See Appendix-I).



Streptomyces sp. OH-4652



Pepticinnamin E

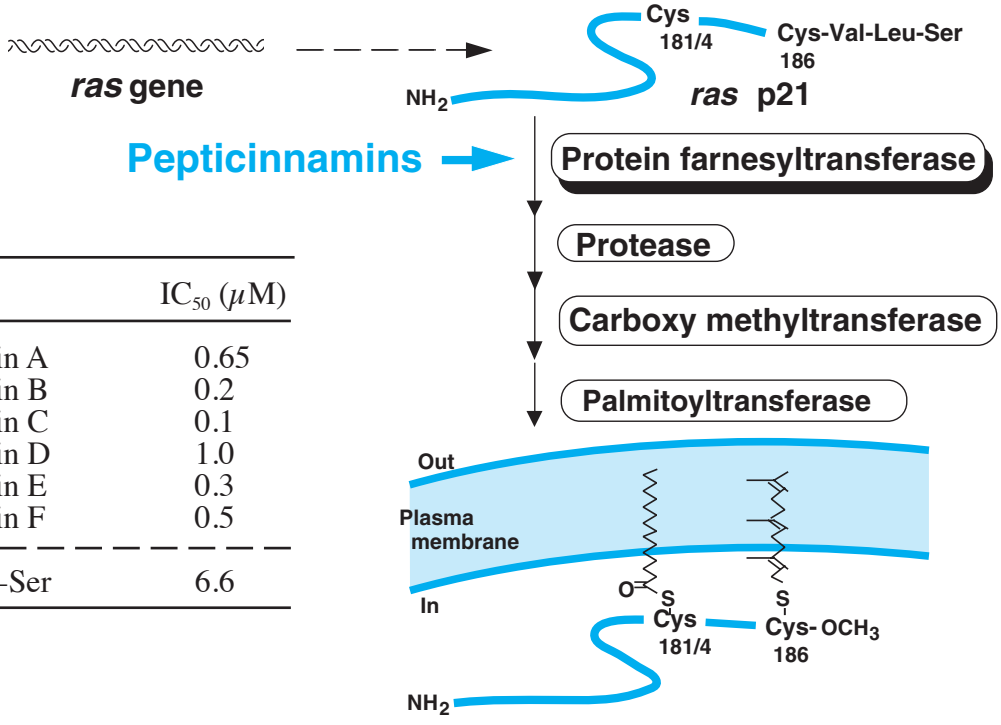
2. Physical data (Pepticinnamin E)

White powder. $C_{49}H_{54}N_5O_{10}Cl$; mol wt 908.46. Sol. in DMSO, MeOH, EtOAc, $CHCl_3$. Insol. in H_2O, hexane.

3. Biological activity[1,3,4,5)]

1) Specific protein farnesyltransferase inhibition

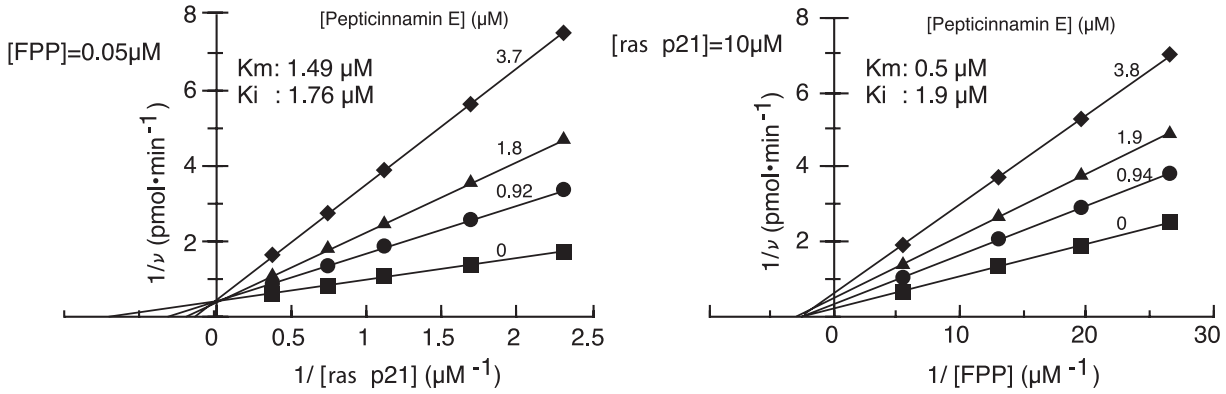
Protein farnesyltransferase catalyses a post-translational modification of ras p21 obligatory for cell transformation of the oncogene protein.



Compound	IC_{50} (μM)
Pepticinnamin A	0.65
Pepticinnamin B	0.2
Pepticinnamin C	0.1
Pepticinnamin D	1.0
Pepticinnamin E	0.3
Pepticinnamin F	0.5
Cys-Val-Leu-Ser	6.6

2) Kinetic analysis of protein farnesyltransferase inhibition by pepticinnamin E

Pepticinnamin E inhibits protein farnesyltransferase competitively with respect to ras p21 and noncompetitively with respect to farnesyl diphosphate (FPP). The K*i* values are shown below.



4. References

1 [498] S. Ōmura *et al*., *J*. *Antibiot*. **46**, 222-228 (1993)
2. [499] K. Shiomi *et al*., *J*. *Antibiot*. **46**, 229-234 (1993)
3. K. Hinterding *et al*., *Angew*. *Chem*. *Int*. *Ed*. **37**, 1236-1239 (1998)
4. [514] H. Takeshima and S. Ōmura, *Tanpakushitsu Kakusan Koso* **38**, 1695-1703 (1993)
5. [554] S. Ōmura and H. Tomoda, *Pure Appl*. *Chem*. **66**, 2267-2270 (1994)