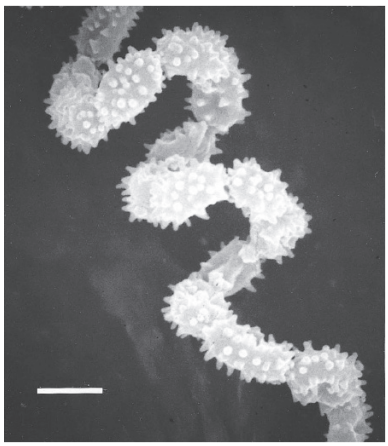
Chloropeptin

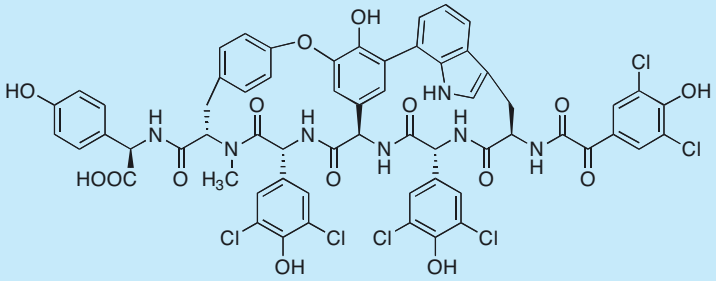
1. Discovery, producing organism and structures[1-4)]

During screening for new gp120-CD4 binding inhibitors from microorganisms, chloropeptins I and II were isolated from the culture broth of the actinomycete strain WK-3419. While the major component, chloropeptin I was identified as a novel compound, chloropeptin II was identified as complestatin[5,6)].

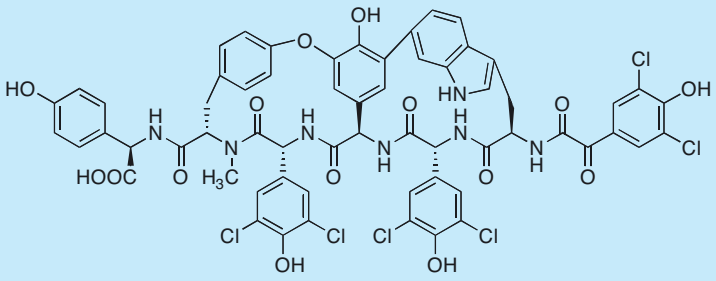
The planer structure of chloropeptin I was elucidated by NMR analysis[1,4)]. The stereostructure was elucidated by NOE experiments in combination with molecular dynamics conformation analysis and Monte Carlo calculations[2)]. The total synthesis of chloropeptin I was reported by Deng *et al*.[8)], Boger *et al*.[9,10,12)] and Zhu *et al*.[11)] (See Appendix I).



Streptomyces sp. WK-3419



Chloropeptin I



Chloropeptin II (Complestatin)

2. Physical data (Chloropeptin I)

Pale yellow brown powder. $C_{61}H_{45}N_7O_{15}Cl_6$; mol wt 1328.79. Sol. in DMSO, MeOH, alkaline H_2O, pyridine. Insol. in H_2O, acetone, $CHCl_3$.

3. Biological activity[1,4,7)]

1) Inhibition of gp120-CD4 binding

Compound	IC_{50} (μM)*
Chloropeptin I	2.0
Chloropeptin II (complestatin)	3.3

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

2) Inhibition of HIV replication in the viral core protein level

Compound	Viral core protein p24 synthesized (ng/ml)		
	Day 2	Day 3	Day 4
None	0	97.3	129.6
Chloropeptin I (7.5 μM)	0	0	7.3

3) Anti-HIV-1 activities of chloropeptin I, complestatin, dextran sulfate, and AZT

Compound	CPE*			Fusion**
	EC_{50} (μM)	CC_{50} (μM)	SI	IC_{50} (μM)
Chloropeptin I	1.6	>600	>380	0.5
Complestatin	1.7	530	320	1.1
Dextran sulfate	2.9 (μg/ml)	>1000 (μg/ml)	>350	2.1 (μg/ml)
AZT	0.011	260	25000	—

* Inhibition effects of chloropeptin I, complestatin, dextran sulfate, and AZT on HIV-1-induced cytopathic effect (CPE) in MT4 cells. The viability of virus- and mock-infected cells was assessed by the MTT method. Anti-CPE effects are expressed as EC_{50} values compared with CC_{50} values of mock-infected control cells. The selectivity index (SI) was the ratio of IC_{50} for CPE to CC_{50}.
** Inhibition effects of chloropeptin I, complestatin, and dextran sulfate on HIV-1-induced syncytia formation in a coculture of virus-infected and uninfected Molt-4 cells. The extent of cell fusion was assayed. Anti-cell fusion effects are expressed as IC_{50} values against the fusion of control cells in the absence of a sample.

4) Antimicrobial activity of chloropeptin I and complestatin assayed by using paper discs

Test organism	Inhibitory zone (ϕ mm)			
	Chloropeptin I		Complestatin	
	1.0	0.25 (mg/ml)	1.0	0.25 (mg/ml)
Staphylococcus aureus FDA 209P	11.3	9.8	11.0	9.7
Micrococcus luteus PCI 1001	13.8	11.0	13.1	10.8
Bacillus subtilis PCI 219	11.1	9.6	11.0	9.4
Acholeplasma laidlawii PG-8 KB 174	12.4*	—	11.0*	—

* hazy zone 50 μl/8 mm disc

4. References

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