IC101, EXTRACELLULAR MATRIX ANTAGONIST PRODUCED BY *Streptomyces* sp. MJ202-72F3

PRODUCTION, ISOLATION, STRUCTURE DETERMINATION AND BIOLOGICAL ACTIVITY

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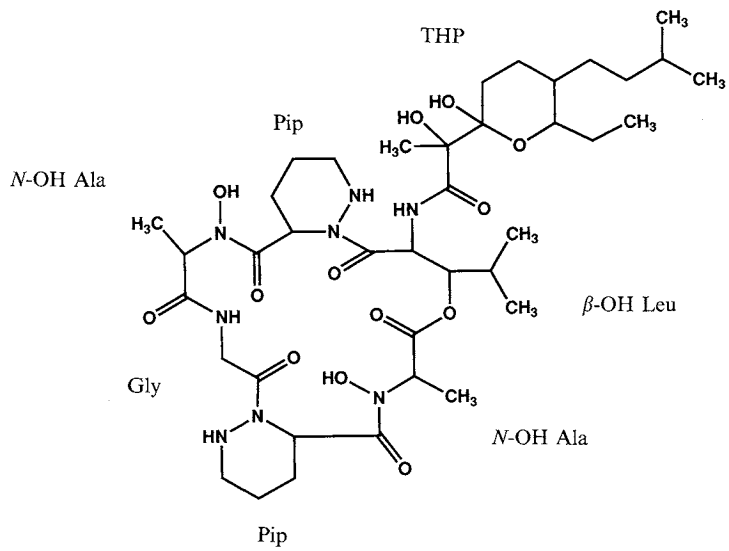
In our search for inhibitors of cell adhesion to components of extracellular matrix (ECM), fibronectin, laminin and collagen type IV, we succeeded in finding a novel cyclic hexadepsipeptide antibiotic, named IC101, which was isolated from cultured mycelium of *Streptomyces albulus* MJ202-72F3. It was purified by centrifugal partition chromatography, preparative reverse phase HPLC and Sephadex LH-20 and was obtained as a white powder. IC101 strongly inhibited cell adhesion to ECM components, suppressed immune responses *in vitro* and *in vivo*, and exhibited antimicrobial activity on Gram-positive bacteria.

In order to develop a new class of immunomodulator or an inhibitor of tumor metastases, we have searched for low molecular weight inhibitors of cell adhesion to components of the ECM in microbial products and found a novel antibiotic, named IC101 (Fig. 1), which was produced together with delaminomycins[1~3] in the cultured mycelium of *Streptomyces* sp. MJ202-72F3. This microorganism was isolated from a soil sample collected in Ohtsuki-shi, Yamanashi Prefecture, Japan. The strain was classified

Fig. 1. Structure of IC101.



as *Streptomyces albulus* MJ202-72F3 by taxonomic studies[1] and deposited in the Fermentation Research Institute of the Agency of Industrial Science and Technology, Japan, with the accession No. FERM P-12674. IC101 strongly inhibited the adhesion of tumor cells to components of the ECM. In this paper, we report the production, isolation, physico-chemical properties, structure elucidation and biological activity of IC101.

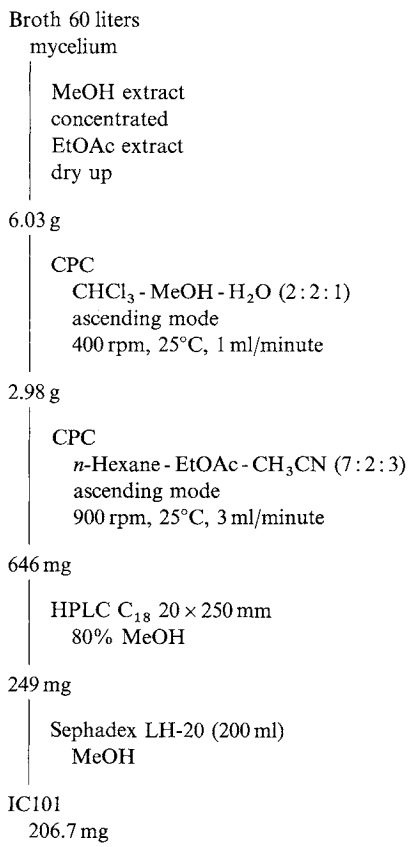
Production and Isolation

The production of IC101 was performed by the method described previously for delaminomycins[1].

The procedure for isolation and purification of IC101 is shown in Fig. 2. The activity of IC101 was assessed using Con A-activated EL4 cells and/or B16 melanoma cells adhesion assay[1]. Each fraction in the process of isolation was diluted with MeOH and assessed.

The cultured broth (60 liters) was centrifuged and the mycelium was harvested. The mycelium was extracted twice with five volumes of MeOH per wet weight of mycelium. The extract was concentrated under reduced pressure to give an aqueous solution. This was extracted twice with EtOAc and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material (6.03 g) was subjected to centrifugal partition chromatography (CPC, Sanki Engineering) previously equilibrated with the lower layer of $CHCl_3$ - MeOH - H_2O (2 : 2 : 1) at 25°C, 400 rpm. IC101 was retained in the immobile phase in the ascending mode, then eluted with the lower layer of $CHCl_3$ - MeOH - H_2O (2 : 2 : 1) in descending mode and evaporated under reduced pressure. The fraction containing IC101 was injected into the CPC which had been previously equilibrated with the lower layer of *n*-hexane - EtOAc - CH_3CN (7 : 2 : 3) at 25°C, 900 rpm. IC101 was retained in the immobile phase in ascending mode, and was eluted with the lower layer of *n*-hexane - EtOAc - CH_3CN (7 : 2 : 3) in the descending mode. After concentration under reduced pressure, the residue was applied to a reverse phase HPLC column and eluted with 80% MeOH. Active fractions containing IC101 were collected and concentrated under reduced pressure, and then loaded on to a Sephadex LH-20 column and eluted with MeOH. The active fractions were concentrated to dryness; 206.7 mg of IC101 was obtained as a white powder. The purity of isolated IC101 was assessed by silica gel TLC using 2-PrOH - NH_4OH - H_2O = 9 : 1 : 2 as a solvent and reverse phase HPLC using MeOH - H_2O = 8 : 2 as a mobile phase. IC101 showed a single spot at Rf 0.66 on a silica gel plate by spraying Rydon-Smith reagent or Vanillin - H_2SO_4. In reverse phase HPLC, the purity of IC101 showed in excess of 97% by UV detection at 235 nm

Fig. 2. Purification of IC101.



(Column: Shiseido CAPCELL PAK C_{18}, 250 × 4.6 mm i.d.; flow rate: 1.0 ml/minute; temperature: 35°C).

Physico-chemical Properties and Structure Elucidation

The physico-chemical properties of IC101 are summarized in Table 1.

IC101 is positive to Rydon-Smith, vanillin - H_2SO_4 reagents and negative to ninhydrin and Dragendorff reagents.

In the infrared spectrum, IC101 showed absorption maxima at 3400 cm^{-1} (OH and/or NH), 1640 and 1540 cm^{-1} (amide). The spectrum was typical of certain members of the depsipeptide antibiotics such as Azinothricin[4], A83586C[5], PD124,895[6], PD124,966[6] and L-156,602[7,8]. IC101 appeared to closely resemble L-156,602, which was composed of β-hydroxy leucine (β-OH Leu), glycine (Gly), two of piperazic acid (Pip), two of *N*-hydroxy alanine (N–OH Ala), and tetrahydropyranyl propionic acid (THP). At first, we compared some chromatographic behaviors of IC101 and L-156,602 which had been isolated from a fermentation broth of our strain, MH563-32F1, and identified as L-156,602[8] from the comparison of their physico-chemical properties including NMR, MS and IR spectra.

Both amino acids analyses after 6 N HCl hydrolysis at 110°C for 24 hours showed the same pattern. Both compounds showed the same chromatographic behavior on silica gel TLC (Rf 0.66: 2-PrOH - NH_4OH - H_2O = 9 : 1 : 2; Rf 0.95: $CHCl_3$ - MeOH = 4 : 1). However, IC101 and L-156,602 could be separated from each other by HPLC at the retention times of 14.7 minutes and 11.1 minutes, respectively (Column: Shiseido CAPCELL PAK C_{18}, 250 × 4.6 mm i.d.; mobile phase: MeOH - H_2O (80 : 20); flow rate: 1.0 ml/minute; detection: UV 235 nm; temperature: 35°C).

The molecular formula of IC101 was determined to be $C_{39}H_{66}N_8O_{13}$ based on the HRFAB-MS and ^{13}C NMR spectroscopic information. ^{13}C NMR and the DEPT spectra data of IC101 in C_5D_5N showed a count of carbons (39) and the following carbon types: 8 × CH_3, 9 × CH_2, 3 × CH, 3 × CH_2X, 7 × CHX, 1 × C–O, 1 × O–C–O and 7 × COX. On the other hand, the molecular formula and carbon types (^{13}C NMR data) of L-156,602 were reported as $C_{38}H_{64}N_8O_{13}$ and 8 × CH_3, 8 × CH_2, 3 × CH, 3 × CH_2X, 7 × CHX, 1 × C–O, 1 × O–C–O and 7 × COX, respectively. These facts indicated that the difference between IC101 and L-156,602 is one methylene unit (one carbon and two protons).

The structure of L-156,602 has been determined by X-ray crystallographic analysis. Complete ^1H and ^{13}C NMR assignments for L-156,602 were also reported by HENSENS *et al.*[8]. Thus, the structural elucidation

Table 1. Physico-chemical properties of IC101.

Appearance	White powder
HRFAB-MS Calcd for $C_{39}H_{65}N_8O_{13}$ $(M-H)^-$:	853.4671
Found:	853.4671
Molecular weight	854
Molecular formula	$C_{39}H_{66}N_8O_{13}$
MP	167~170°C
Optical rotation $[\alpha]_D^{27}$ (*c* 0.9, MeOH)	+21°
UV λ_{max}^{MeOH} nm ($E_{1cm}^{1\%}$)	End absorption
IR ν_{max}^{KBr} cm^{-1}	3400, 2960, 1750, 1640, 1520, 1450, 1200, 920
Solubility: Soluble	MeOH, EtOAc, $CHCl_3$,
Insoluble	*n*-Hexane, H_2O
Color reaction: Positive	Rydon-Smith, Vanillin-H_2SO_4
Negative	Ninhydrin, Dragendorff
Rf value on silical gel TLC[a]	0.66

[a] Merck Kieselgel 60 F_{254} Art. 5554 (2-PrOH - NH_4OH - H_2O = 9 : 1 : 2).

Table 2. ^{1}H and ^{13}C NMR chemical shifts of IC101 and L-156,602 in C_5D_5N.

		IC101			L-156,602	
		^{13}C (ppm)	^{1}H (ppm)	$^{1}J_{HH}$ (Hz)		^{13}C (ppm)
β-OH Leu:	NH		8.21 br d	9.0	NH	
	Cα	47.2 d	6.62 m		Cα	47.6 d
	Cβ	80.0 d	5.21 m		Cβ	79.7 d
	Cγ	30.7 d	2.25 m		Cγ	30.6 d
	Cδ	18.7 q	0.94 d	7.0	Cδ	18.8 q
	Cδ′	20.1 q	0.83 d	7.0	Cδ′	20.0 q
Gly:	NH		7.66 br s		NH	
	Cα	42.5 t	3.86 m, 3.64 br d		Cα	42.6 t
Pip:	NH		5.44 br d	13.2	NH	
	Cα	49.1 d	6.01 m		Cα	49.0 d
	Cβ	25.6 t	2.35 m, ~1.8 m		Cβ	25.7 t
	Cγ	21.9 t	1.86 m, 1.36 m		Cγ	22.0 t
	Cδ	47.6 t	2.99 m, 2.73 m		Cδ	47.7 t
Pip′:	NH		5.04 br d	12.2	NH	
	Cα	49.1 d	6.01 m		Cα	49.6 d
	Cβ	24.5 t	2.02 m, 1.86 m		Cβ	24.2 t
	Cγ	20.9 t	1.43 m, 1.15 m		Cγ	20.8 t
	Cδ	46.7 t	2.73 m, 2.35 m		Cδ	46.6 t
N–OH Ala:	Cα	54.1 d	5.98 br d		Cα	53.6 d
	Cβ	12.3 q	1.57 d	6.9	Cβ	12.4 q
N–OH Ala′:	Cα	54.1 d	5.50 q	7.0	Cα	54.1 d
	Cβ	14.3 q	1.57 d	6.9	Cβ	14.1 q
THP:	C-2	75.9 d	3.70 m		C-2	71.6 d
	C-3	39.6 d	0.94 m		C-3	40.1 d
	C-4	25.0 t	1.60 m, ~1.6 m		C-4	24.4 t
	C-5	28.1 t	2.07 m, ~1.7 m		C-5	28.1 t
	C-6	99.8 s			C-6	100.0 s
	C-7	77.3 s			C-7	76.9 s
	7-CH_3	21.5 q	1.86 s		7-CH_3	21.7 q
	C-1′	29.3 t	1.19 m, 0.86 m		C-1′	39.1 t
	C-2′	35.7 t	1.03 m, 0.86 m		C-2′	31.2 d
	C-3′	28.3 d	1.25 m		C-3′	31.3 t
	C-4′	23.0 q	0.74 d	6.7	C-4′	11.7 q
	C-5′	22.3 q	0.71 d	6.7	2-CH_3	20.2 q
	C-1″	25.7 t	~1.7 m, 1.35 m		2′-CH_3	18.8 q
	1″-CH_3	11.0 q	1.11 t	7.2		
Carbonyl C	COX	170.0 s			COX	169.8 s
		170.2 s				170.2 s
		170.3 s				170.5 s
		170.5 s				170.6 s
		173.1 s				172.9 s
		174.0 s				174.1 s
		177.8 s				178.2 s

^{13}C chemical shifts at 100 MHz, and ^{1}H chemical shifts at 400 MHz were recorded in C_5D_5N at 24~25°C.

of IC101 was carried out by comparing of ^{1}H and ^{13}C NMR spectra including ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, heteronuclear multiple-bond correlation (HMBC) and Homonuclear Hartmann-Hahn (HOHAHA) spectra with those of L-156,602.

In ^{13}C NMR spectra of both compounds, all assigments of residues agreed to within 0.5 ppm with exception of THP moiety as shown in Table 2, indicating the equivalency of sequence and stereochemistry of the common cyclic peptide moiety. The cyclic peptide moiety shown in Fig. 1 is fully consistent with

spectral data, including results of analysis, in the ^1H-^1H COSY, HMBC and HOHAHA spectra of both compounds. The partial structure of IC101 shown in Fig. 3 was thus elucidated by interpretation of the ^1H-^1H COSY, HMBC and HOHAHA spectra. The ^{13}C and ^1H chemical shifts of tetrahydropyranyl ring were almost identical with exception of C-2 carbons (δ 75.9 for IC101 and δ 71.9 for L-156,602). The facts suggested that the molecular difference between IC101 and L-156,602 occurred in the side chains connected to the tetrahydropyranyl ring. The ^1H NMR of IC101 showed the presence of methyl protons at δ 0.71 and δ 0.74 (tentatively named as 4'-H and 5'-H) as doublet signals ($J=6.7$ Hz) indicating the presence of $-CH(CH_3)_2$. In the HMBC spectrum, cross peaks were observed from the methyl protons at δ 0.71 and δ 0.74 to one methine carbon at δ 28.3 (determined as C-3') and one methylene carbon at δ 35.7 (determined as C-2'). Furthermore, a cross peak was observed between 3'-H to methylene carbon at δ 29.3 (determined as C-1'). The connectivity of C-1' and C-3 was confirmed by HOHAHA experiment. On the other hand, the appearance of methyl protons at δ 1.11 (tentatively named as 1''-CH_3) correlated to one methylene carbon at δ 25.7 (determined as C-1'') and one methine carbon at δ 75.9 which can be ascribed to the C-2 methine based on the chemical shifts. Thus, the differences between IC101 and L-156,602 can be ascribed to the side chains of the tetrahydropyranyl ring. The planar structure shown in Fig. 1 was indicated for IC101. ^1H and ^{13}C NMR data of IC101 and L-156,602 in C_5D_5N were shown in Table 2.

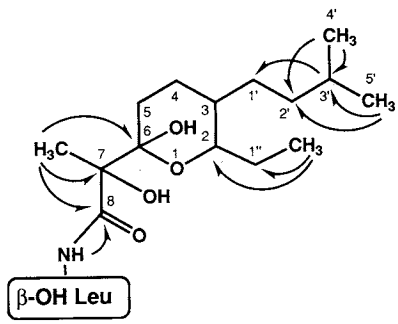
Biological Activity

Inhibition of Cell Adhesion to ECM Components by IC101

Con A-activated EL4 cell adhesion assay: Various amounts of IC101 and EL4 cells (10^5 cells in 100 μl of RPMI-1640 medium containing 1% FCS, 10 mM HEPES and 10 μg/ml of Con A) were added onto the protein-coated microwells and incubated for 1 hour at 37°C in 5% CO_2, 95% air. Each assay was performed in triplicate. As shown in Table 3, IC101 strongly inhibited Con A-activated adhesion of EL4 cells to each ECM component and IC_{50} values were 0.13 μg/ml (laminin) and 0.12 μg/ml (fibronectin).

B16 cell adhesion assay: B16 cells were maintained in DULBECCO's modified EAGLE's medium (DMEM) supplemented with 10% FCS. IC101 at different concentrations and B16 cells (10^5 in 100 μl of DMEM containing 0.1% BSA and 20 mM HEPES) were added to the ECM protein-coated wells. The plates were incubated for 1 hour at 37°C in 95% air and 5% CO_2. The adhesion assays were carried out in the presence of cycloheximide (20 μg/ml) to minimize the production of endogenous adhesion proteins. Each assay

Fig. 3. Partial structure of THP moiety of IC101.



Arrows indicated long-range ^1H-^{13}C correlations (HMBC).

Table 3. Inhibition of adhesion of Con A-activated EL4 cells and B16 melanoma cells to ECM component by IC101.

Cells	IC_{50} (μg/ml)		
	Fibronectin	Laminin	Collagen type IV
EL4	0.13	0.12	No adherent[a]
B16	0.66	0.51	0.56

[a] Con A-activated EL4 cells do not adhere to collagen type IV.

Table 4. Inhibitory effect of IC101 on MLCR.

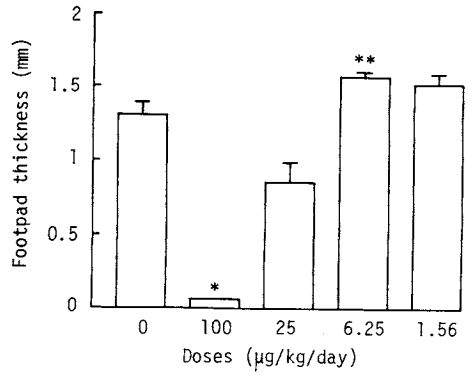
Compound	Dose (μg/ml)	Mean±SD ($\times 10^3$ cpm)	Inhibition (%)	IC_{50} (μg/ml)
IC101	0.16	0.08±0.02	97.8***	
	0.032	0.13±0.03	96.4***	
	0.006	2.31±0.58	36.8**	0.009
	0.001	4.22±0.94	−15.5	
	None	3.65±0.29	0	

*** $P<0.001$ as compared with medium control.
** $P<0.01$.

Table 5. Cytotoxicity of IC101 on tumor cells in cultures.

Tumor cells	L1210	$P388D_1$	B16
IC_{50} (μg/ml)	0.028	0.006	0.031

Fig. 4. Suppressive effect of IC101 on DTH response to SRBC in mice.



IC101 was dissolved in DMSO-tween 80-saline (9:1:90) and given ip daily from days 0 to 4 after immunization. Vehicle (0.25 ml) was given ip as same schedule for drug. * $P<0.001$ and ** $P<0.05$ as compared with vehicle group.

was performed in triplicate.

As shown in Table 3, IC101 strongly inhibited binding of B16 melanoma cells to all ECM components tested. IC_{50} values were between 0.51 and 0.66 μg/ml.

Inhibitory Activity of IC101 on Mixed Lymphocytes Culture Reaction (MLCR)

MLCR assays were performed by the method described previously[1]. Spleen cells (nylon wool-passed) taken from Fisher F344 rats as the responder were mixed with spleen cells (taken from WKY rats as the stimulator) which had been previously incubated with 50 μg/ml of mitomycin C at 37°C for 20 minutes. The mixed cells were cultured with or without drugs in medium containing 10% FCS at 37°C for 5 days in 5% CO_2 in air and [^{3}H]thymidine was added 16 hours before assay. MLCR was determined by measuring the incorporation of [^{3}H]thymidine into the cultured cells. IC101 dissolved in MeOH was diluted with RPMI1640 and added to cultures. Triplicate determinations were made. As shown in Table 4, IC101 inhibited MLCR in a dose dependent manner and the IC_{50} value was 0.009 μg/ml.

Effect of IC101 on Immune Responses to Sheep Red Blood Cells (SRBC) in Mice

The effect of IC101 on immune responses to SRBC in mice was investigated as follows.

Antibody formation: Female CDF_1 mice (10 weeks old) were immunized on day 0 with 1×10^8 SRBC iv. Antibody formation was determined on day 4 by enumerating plaque forming cells (PFC) according to the method described previously[1]. Drug was administrated ip daily from days 1 to 3 after immunization. IC101 in doses of 0.4 to 100 μg/kg did not suppress antibody formation.

Delayed-type Hypersensitivity Response (DTH): CDF_1 mice were immunized iv with 1×10^5 SRBC. Four days later, 1×10^8 SRBC was injected subcutaneously into the left hind footpad. Twenty four hours after the elicitation, footpad thickness was measured with a caliper[1]. Drug was injected ip daily for 5 days starting from the day of immunization. As shown in Fig. 4, IC101 at doses of 25 to 100 μg/kg strongly suppressed the DTH response.

Table 6. Antimicrobial activity of IC101.

Microorganisms	MIC (μg/ml)	Microorganisms	MIC (μg/ml)
Staphylococcus aureus FDA209P	<0.78	*Proteus vulgaris* OX19	>100
S. aureus Smith	<0.78	*Providencia rettgeri* GN311	>100
S. aureus MS9610	<0.78	*Serratia marcescens*	>100
S. aureus No. 5 (MRSA)	<0.78	*Pseudomonas aeruginosa* A3	>50
S. aureus No. 17 (MRSA)	<0.78	*Klebsiella pneumoniae* PCI602	>100
Micrococcus luteus FDA16	<0.78	*Mycobacterium smegmatis* ATCC 607	>100
M. luteus IFO3333	<0.78	*Candida tropicalis* F-1	>100
M. luteus PCI1001	<0.78	*Saccharomyces cerevisiae* F-7	>100
Bacillus anthracis	<0.78	*Cryptococcus neoformans* F-10	>100
B. subtilis NRRL B-558	<0.78	*Cochliobolus miyabeanus*	>100
B. subtilis PCI219	<0.78	*Pyricularia oryzae*	>100
B. cereus ATCC 10702	<0.78	*Pellicularia sasakii*	>100
Corynebacterium bovis 1810	<0.78	*Xanthomonas citri*	>100
Escherichia coli NIHJ	>100	*Trichophyton asteroides* 429	>100
Shigella dysenteriae JS11910	>100	*Aspergillus nigar* F-16	>100
Salmonella typhi T-63	>100		

Cytotoxicity

The cytotoxicity of IC101 on tumor cells is shown in Table 5. Tumor cells were cultured in RPMI-1640 containing 10% FCS with test samples for 72 hours and cytotoxicity was determined by MTT assay. IC101 showed the strongest cytotoxic activity against P388D$_1$ cells and the IC_{50} value was 0.006 μg/ml.

Antimicrobial Activity

Antimicrobial activity of IC101 was examined by the serial agar dilution method using Mueller-Hinton agar (Difco) for antibacterial tests with incubation at 37°C for 18 hours and a nutrient agar containing 1% glucose for antifungal tests with incubation at 27°C for 42 hours. Minimum inhibitory concentration (MIC) value is expressed as the minimum concentration which inhibits growth of the microorganisms. As shown in Table 6, IC101 showed strong antibacterial activity only against Gram-positive bacteria at concentration of lower than 0.78 μg/ml, but not against Gram-negative bacteria nor fungi at 100 μg/ml.

Toxicity

The LD_{50} value of IC101 was found to be between 195 to 390 μg/kg iv to ICR mice.

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