Communications to the Editor

3′-DEOXYTALOPIERICIDIN A_1, A NOVEL ANALOG OF ANTITUMOR ANTIBIOTICS FROM OLIGOTROPH

Sir:

In the course of a screening program for new antitumor substances, we isolated a novel glycopiericidin antibiotic from the mycelial extract of facultative oligotroph[1,2] strain DO-100. Here we report the fermentation, purification, structure determination and antitumor activity of the DO-100 product.

DO-100, probably a *Streptomyces* sp., was isolated from a soil sample collected in Gotemba city, Shizuoka, Japan. For the isolation, agar plates containing 1% Eugon medium (Difco Labs, Detroit, MI, U.S.A.) were used. Colonies were inoculated into 500-ml Erlenmeyer flasks containing 100 ml of normal concentration of Eugon medium, pH 7.2. Sixty inoculated flasks were incubated at 28°C on a rotary shaker at 205 rpm, for 2 days. The antitumor activity was found mainly in the mycelial cake of the culture broth. Fifteen mg of the active substance were finally obtained from 150 g of the mycelial cake through the purification procedure shown in Fig. 1.

The substance was a pale yellow viscous oil. It was soluble in many organic solvents tested and insoluble in water. It changed to a reddish purple with treatment with H_2SO_4, and had two major UV absorption peaks at 235 and 275 nm. FAB-MS analysis showed that the MW was 561 dalton. ^1H NMR and ^{13}C NMR spectra revealed that the substance contained a piericidin A_1 sub-structure[3] including a sugar moiety. The sugar was confirmed to be a methylhexose by 1D homonuclear Hartmann-Hahn experiments, and to be linked at the C-3′ position of piericidin A_1 since the signal of the C-3′ carbon in the ^{13}C NMR spectrum shifted down-field (1.5 ppm) as compared with that of piericidin A_1[3,4]. Fig. 2 shows proton coordination of the sugar as determined by difference-NOE experiments. These data reveal that the biologically active substance is a 3′-deoxytalopiericidin A_1 (DTPA, Fig. 3), which is a new series of glyco-

Fig. 1. Isolation procedure of a DO-100 product.

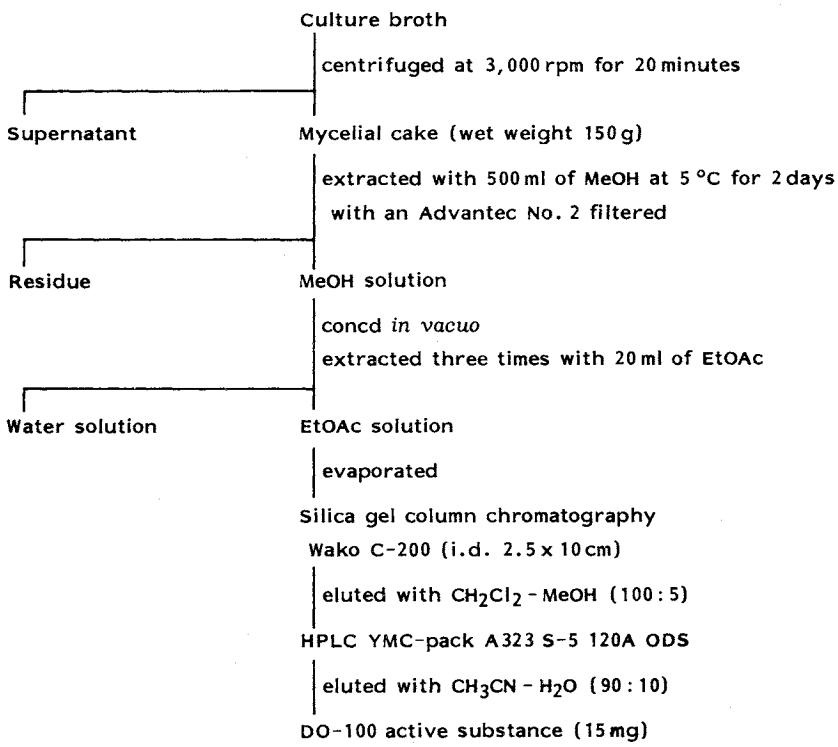


Fig. 2. Proton coordination of the sugar derived from difference-NOE experiments.

The arrows indicate the proton-proton NOE networks.

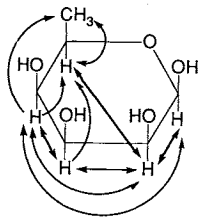
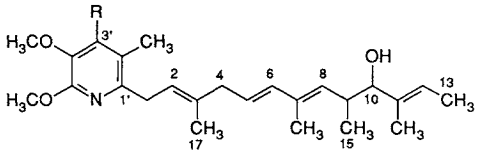
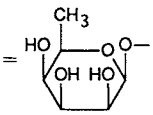


Fig. 3. The structures of DTPA and piericidin A_1.



Piericidin A_1 R = OH

DTPA R =



piericidins[5,6].

As shown in Table 1, DTPA inhibited the proliferation of murine Colon 26 cells ten times more effectively than that of murine leukemia L1210 cells (IC_{50}: 0.81 μg/ml vs 7.91 μg/ml). Known antitumor agents inhibited the proliferation of L1210 cells more effectively than that of Colon 26 cells. In a mouse model, an intraperitoneal injection with 0.625 mg/kg of DTPA also resulted in the suppression of the growth of Colon 26 tumor (T/C = 21.8 %) implanted subcutaneously in syngeneic CDF_1 mice.

Active substances suppressing solid tumors are urgently required for cancer chemotherapy. A further study for a suitable schedule of DTPA therapy is under way using a murine tumor model.

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Table 1. Proliferation inhibition of tumor cells by DTPA and known antitumor agents.

Compound	IC_{50} (μg/ml)[a]		Inhibition rate (b/a)
	Colon 26 (a)	L1210 (b)	
DTPA	0.81	7.91	9.77
5-Fluorouracil	0.26	0.29	1.11
Mitomycin C	0.03	0.02	0.67
Doxorubicin	0.08	0.02	0.25
Cisplatin	0.61	0.09	0.15
Cytosine arabinoside	2.37	0.07	0.03
Nimustin hydrochloride	>20.00	6.73	<0.34
Etoposide (VP-16)	>10.00	0.33	<0.03

[a] Two hundred μl of serial dilutions of each drug were incubated with 5×10^3 tumor cells for 3 days. Cytotoxicity of drugs was assayed by the MTT method[7] and expressed as IC_{50}.

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