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BE-31405, a New Antifungal Antibiotic Produced by *Penicillium minioluteum*

I. Description of Producing Organism, Fermentation, Isolation, Physico-chemical and Biological Properties

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A new antifungal antibiotic, BE-31405, was isolated from the culture broth of a fungal strain, *Penicillium minioluteum* F31405. BE-31405 was isolated by adsorption on high porous polymer resin (Diaion HP-20), followed by solvent extraction, precipitation and crystallization. BE-31405 showed potent growth inhibitory activity against pathogenic fungal strains such as *Candida albicans*, *Candida glabrata* and *Cryptococcus neoformans*, but did not show cytotoxic activity against mammalian cells such as P388 mouse leukemia. The mechanism studies indicated that BE-31405 inhibited the protein synthesis of *C. albicans* but not of mammalian cells.

In the course of our screening program for new antifungal antibiotics, a fungal strain F31405 was found to produce a new antifungal antibiotic designated BE-31405 in whole cell assay. The strain, F31405, was isolated from a soil sample collected in Saitama prefecture, Japan. Based on the cultural properties, strain F31405 was identified as *Penicillium minioluteum*. The active principle was produced both in the mycelium and culture filtrate. BE-31405 was isolated by adsorption on high porous polymer resin (Diaion HP-20), and successively purified by solvent extraction and finally by crystallization. The structure of BE-31405 is shown in Fig. 1. In this paper, the producing strain, fermentation, isolation, physico-chemical and biological properties of BE-31405 are reported.

Description of the Producing Strain

Fungal strain F31405 was isolated from a soil sample collected at Hidaka-cho, Saitama prefecture, Japan. The cultural characteristics on Czapek agar, Czapek yeast extract agar, and malt extract agar are summarized in Table 1. The conidiophore were borne from aerial hyphae and the penicilli were biverticillate. The stipes were smooth or finely rough, $110\sim210\times2.0\sim3.5\,\mu$m. The metulae were $10.0\sim13.0\times2.0\sim3.0\,\mu$m. The phialides were $9.5\sim15.0\times2.0\sim2.5\,\mu$m. The conidia were subspheroidal to ellipsoidal or ovoidal, smooth-walled, $3.5\sim4.5\times2.5\sim3.5\,\mu$m. Scanning Electronmicroscopic picture of strain F31405 is shown in Fig. 2. Based on these characteristics, F31405 was identified as *Penicillium*

Fig. 1. Structures of BE-31405 and sordarin.

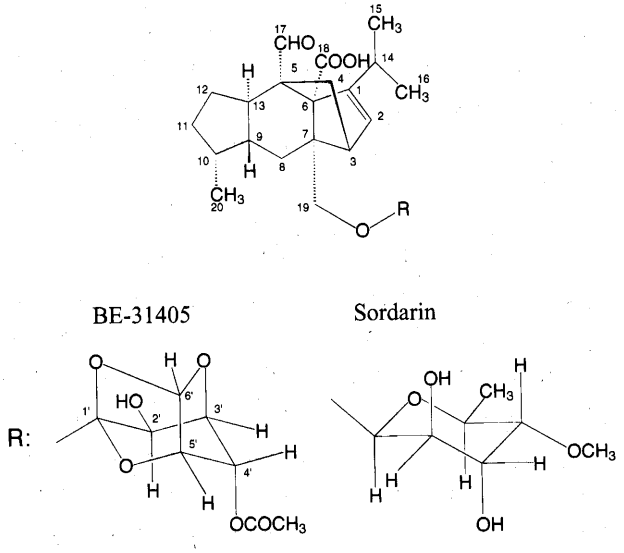
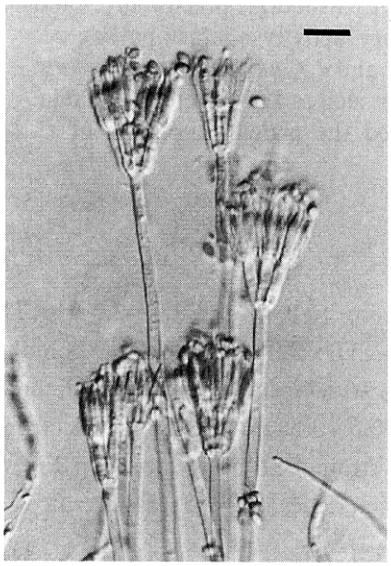


Table 1. Cultural characteristics of F31405 on agar media.

Media	Diameter of colony (mm)	Colony color	Reverse color	Surface of colony
Czapek agar	18~20	Grayish green	White (Center: Orange)	Velvety
Czapek yeast extract agar	20~23	Dark green	Brown (Margin: Orange)	Velvety
Malt extract agar	38~39	Grayish green (Center: Dark green)	Pastel yellow	Velvety

Fig. 2. Photomicrograph of penicilli of strain F31405.

Bar represents 10 μm.



minioluteum[1] and designated *Penicillium minioluteum* F31405.

This strain has been deposited in the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology, Japan as FERM P-15853.

Fermentation

The frozen spores of strain F31405 were inoculated into two 500-ml Erlenmeyer flasks containing 110 ml of the Czapek-Dox broth (pH 6.0 before sterilization) and cultivated on a rotary shaker (180 rpm) at 28°C for 48 hours. Two hundred ml of the seed culture thus obtained was transferred into a 20-liter jar fermenter containing 10 liters of the production medium composed of glucose 7.2%, yeast extract 2.0%, $NaNO_3$ 0.2%, $K_2HPO_4 \cdot H_2O$ 0.1%, $MgSO_4 \cdot 7H_2O$ 0.1%, KCl 0.05%, nicotinic acid 0.5% and KM-75 antifoam (Shin-etsu Chemical Co., Ltd.) 0.03% (pH 6.0 before sterilization). The fermentation was carried out at 28°C for 48 hours under agitation of 400 rpm and aeration of 15 liters/minute. One liter portions of the second seed culture were then transferred into two of 200-liter jar fermenters containing 100 liters of the same production medium. The fermentation was carried out at 28°C for 4 days under agitation of 200 rpm and aeration of 150 liters/minute.

Isolation

The culture broth (220 liters) was filtered with celite and the mycelial cake was extracted with methanol (70 liters). The mycerial extract thus obtained was mixed with the broth filtrate and applied to a high porous polymer resin column (Diaion HP-20, Mitsubishi Kasei Co., 15 i.d. × 80 cm). After washing with 20 liters each of 50% and 70% aqueous methanol, the active principle was eluted with methanol (100 liters). The elute was concentrated *in vacuo* to 6.5 liters and extracted with 4.5 liters of the solvent mixture of ethyl acetate / 2-butanone (1 : 2). The organic layer was evaporated *in vacuo*. The residue was dissolved in methanol (400 ml) and added water (800 ml), then extracted twice with *n*-hexane (800 ml × 2). The aqueous methanol layer was stored at 4°C for 3 days and insoluble material was filtered. The pale brown solid thus obtained was washed with ethanol (500 ml)to give partially purified substance (34.37 g). The ethanol washing was concentrated *in vacuo* to 100 ml and resulting precipitates were filtered to give partially purified substance (15.46 g). Combined partially purified substance (49.83 g) was dissolved in acetone (550 ml) and stirred with small amount of activated charcoal for 1 hour. Activated charcoal was removed by filtration and *n*-hexane (1.3 liters) was added to the acetone

Table 2. Physico-chemical properties of BE-31405.

Appearance	White crystalline powder
Molecular formula	$C_{28}H_{36}O_{10}$
HRFAB-MS (m/z)	
Found:	533.2380 $(M+H)^+$
Calcd:	533.2387
IR (KBr) cm^{-1}	2954, 1738, 1722, 1697, 1323, 1252, 1234, 1095, 1057, 1032, 980, 908
TLC (Rf)[a]	0.30
HPLC (Rt, minutes)[b]	6.21
$[\alpha]_D^{22.5}$	62.6 (c 0.547, MeOH)

[a] Silica gel 60 (F_{254}), Merck; solvent: $CHCl_3$-MeOH (20:1).
[b] Column: Chromatorex ODS (4.6 i.d. × 250 mm); mobile phase: 70 % aqueous methanol; flow rate: 1.0 ml/minute; detection: 220 nm.

Table 3. ^1H NMR data for BE-31405 in $CDCl_3$ (500 MHz).

No.	Chemical shift[a]
2	6.12 (br d, J=3.6)
3	2.83 (t, J=3.6)
4	1.94 (dd, J=12.5, 3.6)
	1.30 (d, J=12.5)
8	1.99 (m), 1.73 (m)
9	1.73 (m)
10	2.07 (m)
11	2.07 (m), 1.23 (m)
12	1.88 (m), 1.02 (m)
13	1.98 (m)
14	2.32 (m)
15	0.95 (d, J=6.8)
16	1.03 (d, J=6.8)
17	9.69 (s)
19	4.01 (d, J=9.6)
	3.96 (d, J=9.6)
20	0.78 (d, J=7.0)
2′	3.69 (d, J=1.2)
3′	4.40 (ddt, J=4.6, 1.5, 1.2)
4′	4.71 (dd, J=4.6, 3.4)
5′	4.74 (ddd, J=3.4, 3.1, 1.5)
6′	5.75 (dd, J=3.1, 1.2)
4′-OAc	2.17 (s)

[a] Multiplicity J in Hz.

solution to make precipitates. By the above procedure, 41.6 g of BE-31405 was obtained as colorless crystalline substance.

Physico-chemical Properties

Physico-chemical properties of BE-31405 are summarized in Table 2. BE-31405 was soluble in methanol and dimethyl sulfoxide (DMSO), but insoluble in *n*-hexane and water. The molecular formula of BE-31405 was established as $C_{28}H_{36}O_{10}$ by HRFAB-MS spectrum and information from NMR. BE-31405 showed no characteristic ultraviolet absorption except of a shoulder at 240 nm. The spectra of ^1H and ^{13}C NMR spectra are shown in Table 3 and 4, respectively. To elucidate the structure, BE-31405 was dissolved in acetone and hydrolyzed with hydrochloride. The acid hydrolysate of BE-31405 was identified as sordaricin. Sordaricin was reported as the aglycon of an antifungal metabolite, sordarin, produced by *Sordaria araneosa*[2~4]. The remaining structure of BE-31405 was revealed as a unique sugar by spectral analyses. The detailed structure determination of BE-31405 will be reported in a separate paper[5].

Table 4. ^{13}C NMR data for BE-31405 in $CDCl_3$ (125 MHz).

No.	Chemical shift	
1	147.3	(s)
2	131.3	(d)
3	46.0	(d)
4	29.2	(t)
5	58.9	(s)
6	71.5	(s)
7	65.1	(s)
8	28.5	(t)
9	41.2	(d)
10	30.8	(d)
11	31.9	(t)
12	26.1	(t)
13	41.6	(d)
14	27.6	(d)
15	22.3	(q)
16	21.0	(q)
17	204.6	(d)
18	176.8	(s)
19	66.9	(t)
20	17.2	(q)
1′	118.4	(s)
2′	66.4	(d)
3′	77.7	(d)
4′	72.2	(d)
5′	74.2	(d)
6′	99.9	(d)
4′-OAc	20.7	(q)
	170.1	(s)

Antifungal and Cytotoxic Activities

Minimum inhibitory concentrations (MIC) were determined by the two-fold serial agar dilution method

Table 5. Minimum inhibitory concentrations (μg/ml) of BE-31405 and sordarin.

Test organism	BE-31405		Sordarin	
	pH 5.4[a]	pH 7.0[b]	pH 5.4[a]	pH 7.0[b]
Candida albicans IFO1270	3.13	50	3.13	100
Candida albicans IFO1385	3.13	50	3.13	50
Candida albicans TIMM3169	3.13	50	3.13	50
Candida albicans TIMM3170	3.13	25	1.56	25
Candida albicans TIMM1768	3.13	50	3.13	50
Candida glabrata TIMM3172	0.78	3.13	50	>100
Candida glabrata TIMM2849	1.56	12.5	100	>100
Candida parapsilosis TIMM3171	>100	>100	>100	>100
Cryptococcus neoformans CR4	6.25	100	100	>100
Cryptococcus neoformans TIMM3173	6.25	50	100	>100
Cryptococcus neoformans TIMM3174	12.5	50	>100	>100
Endomyces ovetensis IFO1201	>100	>100	>100	>100
Saccharomyces cerevisiae IFO0283	3.13	50	1.56	25
Schizosaccharomyces pombe IAM4863	0.78	6.25	100	>100
Trichosporon cutaneum IFO1198	>100	>100	>100	>100
Aspergillus niger IFO31012	>100	>100	>100	>100
Penicillium chrysogenum IFO6223	6.25	100	>100	>100

MIC were determined using agar dilution method in Yeast Nitrogen Base (Difco) containing 1% glucose[a] or using the same medium adjusted pH at 7.0 with 0.25% K_2HPO_4[b] at 28°C for 3 days.

using Yeast Nitrogen Base (Difco) containing 1% glucose (pH 5.4, YNBG) or the same medium adjusted pH at 7.0 with 0.25% K_2HPO_4. Sordarin was isolated from the culture broth of *Sordaria araneosa* ATCC36386 to compare antifungal activity of BE-31405 and sordarin. Table 5 suggested that the antifungal activities of BE-31405 and sordarin were 4 to 20 times stronger at pH 5.4 than at pH 7.0. In acidic condition, both compounds showed potent growth inhibition against several strains of *C. albicans*, and *Saccharomyces cerevisiae* IFO 0283. *C. glabrata*, *C. neoformans*, *Schizosaccharomyces pombe* and *Penicillium chrysogenum* were susceptible to BE-31405 (MIC at pH 5.4: 0.78~12.5 μg/ml) but resistant to sordarin (MIC at pH 5.4: 50~100 μg/ml). The MIC of BE-31405 against *C. albicans* IFO1385 (1.56 μg/ml) was between those of amphotericin B (0.39 μg/ml) and miconazole (6.25 μg/ml), when the MIC was determined on Yeast Morphology agar (Difco). BE-31405 and sordarin showed no antifungal activity against *Aspergillus niger* and showed no antibacterial activity against gram positive and negative bacteria, such as *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Serratia marcescens*.

The cytotoxicity of BE-31405 against P388 mouse leukemia cell line was examined by the method previously reported[6]. BE-31405 did not show 50% growth inhibition against P388 even at a dose of 50 μg/ml.

Effects on Protein Synthesis

Table 6 shows the effects of BE-31405 and cycloheximide on cell-free protein syntheses in *C. albicans*, *S. cerevisiae* and rabbit reticulocyte. The polysome directed incorporation of tritium-labeled leucine into TCA precipitatable material was measured essentially according to the method reported by TUITE *et al.*[7]. The polysome-free lysate (OD_{260}: 3) prepared from spheroplast was mixed with polysome (OD_{280}: 2) in 16 mM HEPES-KOH (pH 7.4) buffer containing KOAc 40 mM, $Mg(OAc)_2$ 2 mM, ATP 0.4 mM, GTP 0.08 mM, creatine phosphate 20 mM, creatine phosphokinase 64 μg/ml, glycerol 4.8%, dithiothreitol 1.7 mM, $CaCl_2$ 0.08 mM, 50 μg/ml each of amino acids except leucine, and 80 μCi/ml of L-[4,5-^{3}H]-leucine to make the reaction mixture (50 μl). After incubation at 30°C for 10 minutes in the presence or absence of test samples dissolved in DMSO at a final concentration of 0.2%, labeled proteins were precipitated by incubation with ice-cold 5% TCA for 10 minutes, and harvested on GF/C glass filter (Whatman). The filter was dried and counted in a liquid scintillation spectrometer. The poly-uridine directed incorporation of L-[2,3,4,5-^{3}H]-phenylalanine into TCA precipitatable material was measured essentially according to the above method except that amino acids were excluded from reaction mixture, and L-[2,3,4,5-^{3}H]-

Table 6. IC_{50} (μg/ml) of BE-31405 and cycloheximide against incorporation of labeled amino acid into TCA insoluble materials in cell free protein synthesis.

Source	Template/Labeled AA	BE-31405	Cycloheximide
C. albicans IFO1385[a]	polysome/Leu[b]	<0.04	>100
	poly U/Phe[c]	<0.04	>100
S. cerevisiae IFO0283[a]	polysome/Leu[b]	0.62	1.88
	poly U/Phe[c]	1.18	<0.10
Rabbit reticulocyte[d]	synthesized RNA[e]/Leu[b]	>100	0.18

[a] Polysome-free lysate prepared from spheroplast, [b] L-[4,5-^{3}H]-leucine, [c] L-[2,3,4,5-^{3}H]-phenylalanine, [d] rabbit reticulocyte lysate (Retic Lysate IVT™ Kit), [e] *in vitro* synthesized capped RNA which coded for *Xenopus* elongation factor 1-α.

Table 7. IC_{50} (μg/ml) of BE-31405 against incorporation of amino acids into TCA insoluble materials in intact *C. albicans*.

pH	Labeled amino acid			
	L-[4,5-^{3}H]-Leu	L-[4,5-^{3}H]-Ile	L-[2,3-^{3}H]-Ala	L-[2,3-^{3}H]-Arg
5.4[a]	6.3	3.1	0.3	10.5
7.0[b]	>20	>20	>20	>20

[a] Yeast Nitrogen Base (Difco) containing 1% glucose (pH 5.4).
[b] The same medium adjusted pH at 7.0 with 0.25% K_2HPO_4.

phenylalanine (80 μCi/ml) and poly-uridine (400 μg/ml) were added instead of L-[4,5-^{3}H]-leucine and polysome, respectively. The rabbit reticulocyte cell-free protein synthesis was assayed by using Retic Lysate IVT™ Kit (Ambion). Reticulocyte lysate and L-[4,5-^{3}H]-leucine (1.0 mCi/ml) were incubated with *in vitro* synthesized capped RNA which coded for *Xenopus* elongation factor 1-α at 30°C for 60 minutes. Radiolabelled proteins were precipitated by incubation with the mixture of sodium hydroxide, unlabelled amino acid and hydrogen peroxide. The precipitatable material was harvested on GF/C glass filter (Whatman) after TCA treatment and then counted. As shown in Table 6, cycloheximide strongly inhibited the cell-free protein synthesis of *S. cerevisiae* and rabbit reticulocyte but did not inhibit that of *C. albicans*. In contrast, BE-31405 strongly inhibited *C. albicans* and *S. cerevisiae* cell-free protein syntheses, but did not inhibit rabbit reticulocyte cell-free protein synthesis.

The effects of BE-31405 on the protein synthesis in the whole cell of *C. albicans* were determined by measuring incorporation of tritium-labeled amino acids into TCA insoluble material (Table 7). *C. albicans* IFO 1385 (1×10^7 cells/ml) was cultured in YNBG (pH 5.4 or pH 7.0) in the presence of 2 μCi/ml of L-[4,5-^{3}H]-leucine, L-[4,5-^{3}H]-isoleucine, L-[2,3-^{3}H]-alanine or L-[2,3-^{3}H]-arginine at 30°C for 2 hours. The cell suspension (100 μl) was filtrated with glass fiber filter (MultiScreen Assay System, Millipore). After washing 3 times each with 5% TCA and saline, the radioactivity remaining on the filter was counted. BE-31405 strongly inhibited incorporation of all of the tested labeled-amino acids when *C. albicans* was cultured at pH 5.4 (IC_{50}=0.3 to 10.5). However, 20 μg/ml of BE-31405 did not inhibit the incorporation of labeled-amino acid into intact *Candida* cultured at pH 7.0.

Discussion

The incidence of life-threatening fungal infections has steadily increased in immunocompromised hosts such as HIV infected persons and cancer patients[8]. It is well known that *C. albicans* is the major opportunistic pathogen, in addition to this fact, other *Candida* species such as *C. tropicalis*, *C. glabrata*, and *C. krusei* have also been implicated recently. Invasive pulmonary aspergillosis and *Pneumocystis carinii* pneumonia are leading cause of deaths in bone marrow transplant recipients and in HIV-infected patients, respectively. Moreover, resistance to the orally active azoles that are the most

widely used antifungals today is attracting much attention. In particular, *C. glabrata* and *C. krusei* have been recognized as less susceptible than *C. albicans* to azole antifungals such as ketoconazole and fluconazole[9]. Therefore, novel antifungal agents having unique mechanisms of action are continuously required to battle fungal diseases.

BE-31405 consists of two characteristic parts, sordaricin and a unique sugar. Sordaricin structure is a common aglycone of sordarin group antibiotics that include sordarin[2], zofimarin[10], xylarin[11] (SCH57404)[12] and GR135402[13]. The sugar part of BE-31405 is an unusual tricyclic structure and only xylarin (SCH57404) has been reported as the fungal metabolite possessing the similar sugar moiety.

All reported sordarin analogs showed significant anti-*Candida* activity while showed no growth inhibition against mammalian cells *in vitro*. Recently, a study by DOMINGUEZ *et al.* demonstrated that GM237354 acted on elongation factor 2 (EF-2) in fungi[14]. JUSTICE *et al.* reported that sordarin blocked fungal protein synthesis by stabilizing EF-2-ribosome complex in a manner similar to that of fusidic acid[15]. Our mechanism studies also indicated that BE-31405 specifically inhibited fungal cell-free protein synthesis. Interestingly, JUSTICE *et al.* reported that hydrolytic cleavage of sordarin to sordarose and sordaricin abolished antifungal activity and inhibition of protein synthesis *in vitro*, while L-793,422, a sordaricin derivative with an isobutyl ether side chain, retained both activities[15]. MARTINEZ *et al.* suggested that GM237354, one of the most studied semisynthetic sordarin derivatives, had a good anti-*Candida* activity by both oral and subcutaneous administration in rat and mouse candidiasis model[16].

Since BE-31405 has broader antifungal activity against several strains such as *C. glabrata* and *C. neoformans* than other sordarin analogs reported so far, its unique sugar structure may give advantages to the biological activity. Furthermore, BE-31405 retained fairly strong activity against *C. glabrata* at pH 7.0, even though both BE-31405 and sordarin decreased their antifungal activity in neutral condition.

According these results, BE-31405 is expected to be a new lead compound for antifungal agent.

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