PRADIMICINS A, B AND C: NEW ANTIFUNGAL ANTIBIOTICS

II. *IN VITRO* AND *IN VIVO* BIOLOGICAL ACTIVITIES

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Pradimicins A, B and C specify novel antibiotics produced by *Actinomadura hibisca* No. P157-2 (ATCC 53557) possessing potent and broad antifungal activity *in vivo*. They showed moderate *in vitro* antifungal activity against a wide variety of fungi and yeasts including clinically important pathogens, and were highly effective in systemic infection with *Candida albicans* in mice after iv and im administrations. Pradimicin A showed *in vivo* therapeutic activity against *C. albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus* in both normal and immunocompromized mice. 5-Fluorocytosine- and azole-resistant *C. albicans* strains were susceptible to pradimicin A. This antibiotic also demonstrated therapeutic efficacy against lung candidiasis and aspergillosis, vaginal candidiasis and skin *Trichophyton mentagrophytes* infection in mice with iv or topical treatment. The LD_{50} values after a single iv or im administration were 120 mg/kg and more than 400 mg/kg, respectively. Against various cultured mammalian cells, pradimicin A was noncytotoxic at 100 or 500 μg/ml, and showed potent anti-influenza virus activity with an IC_{50} value of 6.8 μg/ml.

In the course of antifungal screening, pradimicins A, B and C were found in the culture of *Actinomadura hibisca* No. P157-2 (ATCC 53557)[1~4] and their chemical structures were determined to be a benzo[*a*]naphthacenequinone substituted by a D-alanine and sugars[4~7]. This paper describes their *in vitro* and *in vivo* antifungal activities. Pradimicin A has been extensively evaluated for *in vivo* therapeutic activity in a variety of murine systemic and local fungal infections, for acute toxicity in mice and for other biological activities.

Materials and Methods

Antifungal Agents

Pradimicins A, B and C were prepared at Bristol-Myers Research Institute Co., Tokyo and used after dissolving in saline containing 10% DMSO and adjusting to pH 7.5 with 1.0 N NaOH. Amphotericin B (Fungizone, sodium deoxycholate complex) was purchased from Squibb, Japan and used by dissolving in saline for both *in vitro* and *in vivo* experiments. Ketoconazole was obtained from Janssen Pharmaceuticals and used as a suspension in saline containing 10% DMSO. 5-Fluorocytosine purchased from Sigma Chemical Company was dissolved in saline.

In Vitro Antifungal Activity

The MICs of the antifungal agents were determined by an agar dilution method on yeast morphology agar adjusted to pH 7.0 with 1/15 M phosphate buffer. A 5-μl aliquot of fungal suspension containing 10^6 cells/ml, except for *Trichophyton mentagrophytes* No. 4329 which contained 10^7 cells/ml, was inoculated onto the surface of the antibiotic-containing agar plates with a multiinoculator. After incubation at 28°C for 40 hours, the lowest concentration of antibiotic causing virtually complete inhibition of fungal growth

† Deceased.

(MIC) was determined.

In Vivo Antifungal Activity

Systemic Fungal Infections in Normal Mice: The *in vivo* therapeutic efficacy of pradimicins A, B and C was examined comparatively with amphotericin B and ketoconazole against systemic infection with *C. albicans* A9540 (10^6 cells/mouse), 5-fluorocytosine-resistant *C. albicans* YA22851 (5.5×10^5 cells/mouse), azole-resistant *C. albicans* YA26090 (8.8×10^5 cells/mouse), *Cryptococcus neoformans* IAM 4514 (10^6 cells/mouse) or *Aspergillus fumigatus* IAM 2034 (10^7 cells/mouse) in normal mice. *C. albicans* and *C. neoformans* were cultured at 28°C for 18 and 48 hours, respectively, in YGP medium (glucose 1.5%, peptone 1.0%, yeast extract 0.4%, K_2HPO_4 0.05% and $MgSO_4 \cdot 7H_2O$ 0.05%, pH 7.0) and suspended in saline. *A. fumigatus* was cultured at 28°C for 7 days on YGP agar slant and the spores were suspended in saline. Male ICR mice weighing 20 to 24 g were infected iv with approximately 10 times the median lethal doses of each fungus as shown above. Groups of 5 mice at each dose level were given the test compounds by iv or im dosing route. The initial treatment was given immediately after the fungal challenge. The 50% protection dose (PD_{50}) was calculated by the method of LITCHFIELD and WILCOXON[8] from the survival rate recorded 20 days after the fungal challenge. Untreated animals died 7 to 15 days post infection.

Systemic Fungal Infections in Immunocompromized Mice: Groups of 5 male ICR mice weighing 20 to 24 g were treated ip with 200 mg/kg of cyclophosphamide 4 days before *C. albicans* A9540, *Candida tropicalis* CS-07, *C. neoformans* IAM 4514 or *A. fumigatus* IAM 2034 iv infection at 2.2×10^5, 2.3×10^6, 2.9×10^5 or 2.0×10^6 cells/mouse (10 times LD_{50}), respectively. Test compounds were administered iv or im to the mice. The initial treatment was done immediately after the fungal challenge.

Lung *C. albicans* and *A. fumigatus* Infections: Groups of 4 male ICR mice weighing 20 to 25 g were treated ip with 200 mg/kg of cyclophosphamide 4 days before the lung infection with *C. albicans* A9540 or *A. fumigatus* IAM 2034. The mice were anesthetized with ether and were infected with a 70-μl of *C. albicans* or *A. fumigatus* cell suspension containing 1×10^6 or 1.1×10^8 cells, respectively, through an intranasal route on day 0. Test compounds were administered iv to the mice immediately after the inoculation followed by once a day administration on days 2 and 4. The PD_{50} was calculated from the survival rate recorded 20 days after the fungal challenge.

Vaginal *C. albicans* Infection: Groups of 5 female ICR mice weighing 20 to 24 g were treated sc with 0.5 mg/kg of estradiol benzoate 3 days before and 2 days after vaginal infection with *C. albicans* A9540. A 10-μl portion of a cell suspension of *C. albicans* containing 10^6 cells was inoculated intravaginally on day 0. Test compounds were administered im to the mice immediately after the inoculation followed by once a day for 4 days. On day 7, vaginal exudate was sampled with a thin glass rod and spread on an YGP agar plate containing 100 μg/ml of chloramphenicol. The plate was incubated at 28°C for 2 days. Viable cell count was made and graded by the scores indicated in Table 1.

Skin *T. mentagrophytes* Infection: Groups of 5 male ICR mice weighing 20 to 25 g were anesthetized ip with 35 mg/kg of pentobarbital. After removing the hair from the back (approx 2 cm^2), the skin was gently injured with sandpaper and vaccination needles. A 100-μl sample of cell suspension of *T. mentagrophytes* No. 4329 containing 5×10^5 cells was applied to the injured skin on day 0. Test compounds were mixed with Solbase (50% macrogol 400, Dainippon Pharmaceutical Co.) and topically spread around the infected area with a glass rod (once a day on days 0 to 4). On the day 7, lesions of the infected area were graded according to the severity of the infection by the scores indicated in Table 2.

Table 1. Scores of vaginal *Candida albicans* infection in mice.

Number of cells/plate	Score
>459	4
458～146	3
145～47	2
46～15	1
14～0	0

Table 2. Lesion scores of skin *Trichophyton mentagrophytes* infection in mice.

Severity of infection	Score
Erythema and confluent scaling and whitish patches	4
Erythema and numerous whitish area	3
Erythema with whitish area	2
Erythema	1
Normal	0

In Vitro Cytotoxicity

Madin Darby canine kidney (MDCK), green monkey kidney (Vero) and murine melanoma (B16-F10) cells were grown to the logarithmic phase in Eagle minimum essential medium (MEM) supplemented with fetal calf serum (FCS, 10% in MDCK and B16-F10 cells, and 5% in Vero cells) and antibiotic (50 μl/ml of amikacin in MDCK and Vero cells, and 60 μg/ml of kanamycin in B16-F10 cells). Human colon carcinoma (HCT-116) cells were grown in McCoy's 5A medium supplemented with FCS (10%), benzylpenicillin (100 U/ml) and streptomycin (100 μg/ml) at 37°C in a humidified atmosphere of 5% CO_2 and 95% air. MDCK cells were obtained from the American Type Culture Collection (Rockville, MD) and the other cell lines were from Bristol-Myers Squibb Company (Wallingford, CT). MDCK, Vero, B16-F10 and HCT-116 cells were harvested and a 180-μl aliquot of cell suspension was implanted into wells of a 96-well microplate at the inoculum sizes of 1×10^5, 1×10^5, 3×10^4 and 6×10^4 cells/ml, respectively, and incubated for 24 hours. After adding test compounds (20 μl), they were further incubated for 72 hours. The cytotoxicity was colorimetrically determined at 540 nm after staining viable cells with 0.006% neutral red solution.

Acute Toxicity in Mice

Pradimicin A was dissolved in saline containing 10% DMSO. The test compound solution was adjusted to pH 7.5 with 1.0 N NaOH and injected iv or im once to groups of 5 male ICR mice at a dose volume of 0.2 ml per 10 g body weight. The animals were observed daily for 10 days for physical and behavioral signs of toxicity.

In Vitro Antiviral Activity Determined by the Plaque Reduction Assay

MDCK and Vero cells were grown in Eagle MEM supplemented with FCS (10% for MDCK cells, 5% for Vero cells) and 50 μg/ml of amikacin. Influenza virus type A Victoria and herpes simplex virus type 1 (HSV-1) KOS strains were grown on MDCK and Vero cells, respectively. In the anti-influenza virus assay, confluent MDCK cell monolayers were grown in a 12-well microplate and the medium drained from the culture and washed with Eagle MEM. The culture was infected with 20 ~ 30 pfu/well of the virus in Eagle MEM containing trypsin. After adsorption for 1 hour at 37°C, unadsorbed viruses were removed and 2 ml of an overlay of Eagle medium with 0.25% agarose containing 2-fold dilutions of test compound were added. The culture was incubated at 37°C in a humidified atmosphere of 5% CO_2 and 95% air for 48 ~ 72 hours until the plaques were observed. After removing the overlay medium, cell monolayers were fixed with 10% formaldehyde solution and the plaques were counted. In the anti-HSV assay, Vero cell monolayers were grown in a 24-well microplate and the medium was drained from the culture, which was washed with Eagle MEM. The cultures were inoculated with approximately 50 pfu/well of HSV-1. After adsorption for 1 hour at 37°C, unadsorbed viruses were removed and the cultures were overlayed with 1 ml of Eagle MEM containing 0.3% immune serum globulin and 2-fold dilutions of the test compound. The cultures were incubated at 37°C for 48 ~ 72 hours until the plaques were observed. After removing overlay medium, cell monolayers were stained with carbol-fuchsin and the plaques were counted.

Results

In Vitro Antifungal Activity

MICs for pradimicins A, B and C, amphotericin B and ketoconazole against 16 different fungi and yeasts are shown in Table 3. Pradimicin A showed weaker activity than amphotericin B but inhibited a wide range of fungi and yeasts tested with MIC values of 0.8 ~ 12.5 μg/ml except for *Mucor spinosus* which showed no susceptibility at 100 μg/ml. Both pradimicins B and C exhibited similarly broad antifungal spectra while no or weak inhibition was seen against *Fusarium moniliforme*, *Petriellidium boydii* or *M. spinosus*. All pradimicins possessed significantly stronger anti-*Candida* activity than ketoconazole.

In Vivo Antifungal Activity against Systemic Infections in Mice

In vivo anti-*Candida* activity of pradimicins A, B and C was examined in the systemic *C. albicans*

Table 3. Antifungal spectrum of pradimicins A, B and C by an agar dilution method[a].

Test organism	MIC (μg/ml)				
	Pradimicins			Amphotericin B	Ketoconazole
	A	B	C		
Saccharomyces cerevisiae ATCC 9763	3.1	0.8	3.1	0.2	<0.05
Candida albicans IAM 4888	6.3	3.1	3.1	0.4	50
C. albicans A9540	6.3	3.1	3.1	0.4	50
C. albicans ATCC 32354	3.1	3.1	1.6	0.4	25
C. albicans 83-2-14	12.5	3.1	3.1	0.4	25
C. tropicalis 85-8	12.5	6.3	3.1	0.4	50
Cryptococcus neoformans D49	1.6	0.8	1.6	0.2	0.4
C. neoformans IAM 4514	1.6	1.6	1.6	0.2	0.2
Aspergillus fumigatus IAM 2530	1.6	3.1	1.6	0.4	6.3
A. fumigatus IAM 2034	1.6	3.1	1.6	0.4	6.3
A. flavus FA 21436	6.3	6.3	3.1	6.3	3.1
Fusarium moniliforme A2284	6.3	>100	50	1.6	25
Trichophyton mentagrophytes No. 4329	3.1	3.1	3.1	0.8	0.8
Sporothrix schenckii IFO 8158	0.8	3.1	0.8	0.8	1.6
Petriellidium boydii IFO 8078	6.3	>100	100	6.3	0.8
Mucor spinosus IFO 5317	>100	6.3	100	0.1	100

[a] Yeast morphology agar adjusted to pH 7.0 with 1/15 M phosphate buffer.

Table 4. *In vivo* antifungal activity of pradimicins A, B and C against systemic infection with *Candida albicans* A9540 in mice (n=5).

Compound	PD_{50}[a] (mg/kg/dose)	
	Single iv	Bid × 2 im[b]
Pradimicin A	7.9	21
Pradimicin B	11	22
Pradimicin C	14	16
Amphotericin B	0.22	0.28
Ketoconazole	44	95

[a] PD_{50} value was calculated on day 20 after the fungal challenge.
[b] Bid × 2: See a footnote.
Inoculum size: $10LD_{50}$.

Table 5. *In vivo* antifungal activity of pradimicin A against systemic *Candida albicans* infections with 5-fluorocytosine- and azole-resistant strains in mice (n=5).

Compound	PD_{50}[a] (mg/kg/dose, single iv)	
	C. albicans	
	YA22851[b]	A26090[c]
Pradimicin A	7.2	5.6
Amphotericin B	0.15	0.56
Ketoconazole	>50	>50
5-Fluorocytosine	>100	>100

[a] PD_{50} value was calculated on day 20 after the fungal challenge.
[b] 5-Fluorocytosine-resistant *C. albicans*.
[c] Azole-resistant *C. albicans*.
Inoculum size: $10LD_{50}$.

A9540 infection in mice by iv (single[†]) or im (bid × 2[†]) administration. The results are summarized in Table 4. Pradimicins A, B and C were active against systemic candidiasis with PD_{50} values of 7.9 ~ 14 mg/kg iv and 16 ~ 22 mg/kg/dose im. They were 3 ~ 6 times more potent than ketoconazole but 30 ~ 80 times less potent than amphotericin B. Against 5-fluorocytosine- and azole-resistant *C. albicans* infections, both pradimicin A and amphotericin B were effective at the same dose level by a single iv administration as they were against sensitive *C. albicans* A9540 infection (Table 5). Ketoconazole and 5-fluorocytosine were inactive against both resistant *Candida* strains at 50 and 100 mg/kg iv, respectively.

[†] Treatment schedules of test compounds, single: Once on day 0, bid × 2: twice a day on days 0 and 1, q2d × 3: once a day on days 0, 2 and 4, qd × 5: once a day on days 0 ~ 4 after fungal challenge.

Table 6. *In vivo* antifungal activity of pradimicin A against systemic *Cryptococcus* and *Aspergillus* infections in mice (n=5).

Compound	PD_{50}[a] (mg/kg/dose)			
	C. neoformans IAM 4514		*A. fumigatus* IAM 2034	
	Single iv	Bid × 2 im	Single iv	Bid × 2 im
Pradimicin A	8.9	4.5	21	22
Amphotericin B	0.30	0.35	0.42	0.20
Ketoconazole	35	>100	45	84

[a] PD_{50} value was calculated on day 20 after the fungal challenge.
Inoculum size: $10LD_{50}$.

Table 7. Antifungal activity of pradimicin A in immunocompromized mice[a] (n=5).

Compound	PD_{50}[b] (mg/kg/dose)				
	C. albicans A9540		*C. tropicalis* CS-07 (Single iv)	*C. neoformans* IAM 4514 (Single iv)	*A. fumigatus* IAM 2034 (Single iv)
	Single iv	Bid × 2 im			
Pradimicin A	28	22	7.7	19	45
Amphotericin B	0.56	0.33	0.28	0.56	0.65

[a] Mice were pretreated ip with 200 mg/kg of cyclophosphamide 4 days prior to the infection.
[b] PD_{50} value was calculated on day 20 after the fungal challenge.
Inoculum size: $10LD_{50}$.

By single iv and bid × 2 im administrations, pradimicin A also showed significant protective effects on systemic infections with *C. neoformans* IAM 4514 and *A. fumigatus* IAM 2034 in mice with PD_{50} values of 8.9 and 21 mg/kg iv, and 4.5 and 22 mg/kg/dose im, respectively (Table 6). Pradimicin A exhibited good therapeutic efficacy in immunocompromized mice infected systemically with *C. albicans* A9540, *C. tropicalis* CS-07, *C. neoformans* IAM 4514 and *A. fumigatus* IAM 2034 infections by a single iv dose, the PD_{50} values being 28, 7.7, 19 and 45 mg/kg, respectively (Table 7). Anti-*C. albicans* activity of pradimicin A was also seen with bid × 2 im treatment.

Table 8. Antifungal activity of pradimicin A against *Candida* and *Aspergillus* lung infections in mice (n=5).

Compound	PD_{50}[a] (mg/kg/dose, q2d × 3 iv)	
	C. albicans A9540	*A. fumigatus* IAM 2034
Pradimicin A	18	23
Amphotericin B	0.71	0.30

[a] PD_{50} value was calculated on day 20 after the fungal challenge.
Inoculum size: $10LD_{50}$.

In Vivo Antifungal Activity against Lung Infections in Mice

Pradimicin A and amphotericin B were tested for therapeutic effects on murine lung infections with *C. albicans* A9540 and *A. fumigatus* IAM 2034 by an intravenous q2d × 3 dosing schedule. As summarized in Table 8, both pradimicin A and amphotericin B significantly protected against lethality of mice with lung candidiasis and aspergillosis, the PD_{50} values of pradimicin A being 18 and 23 mg/kg/dose, respectively.

In Vivo Antifungal Activity against Vaginal and Skin Infections in Mice

The therapeutic efficacy of pradimicin A and amphotericin B was compared against vaginal infec-

Table 9. Antifungal activity of pradimicin A against *Candida* vaginal and *Trichophyton* skin infections in mice (n = 5).

Compound	*C. albicans* A9540 vaginal infection		*T. mentagrophytes* No. 4329 skin infection
	ED_{50} (mg/kg/dose, iv)	EC_{50} (% topical)	EC_{50} (% topical)
Pradimicin A	24	0.33	1.7
Amphotericin B	0.39	0.10	0.70

In both iv and topical treatments, test compounds were administered by qd × 5 schedule and their ED_{50} or EC_{50} values were calculated on day 7 after the fungal challenge.

tion with *C. albicans* A9540 by qd × 5 iv and topical treatments in mice. As shown in Table 9, intravenously administered pradimicin A and amphotericin B significantly inhibited vaginal *Candida* infection with PD_{50} values of 24 and 0.39 mg/kg/dose, respectively. Both compounds were active but much weaker than ketoconazole by topical treatment. Against skin infection with *T. mentagrophytes* No. 4329, topical pradimicin A was also effective with an EC_{50} value of 1.7%.

Table 10. *In vitro* cytotoxicity of pradimicin A against various mammalian cells.

Cell	IC_{50} (μg/ml)
Vero	>100
MDCK	>100
HCT-116	>500
B16-F10	>500

Medium: Eagle MEM supplemented with FCS (10% for MDCK and B16-F10 cells, and 5% for Vero cells) and antibiotic (50 μg/ml of amikacin for MDCK and Vero cells, and 60 μg/ml of kanamycin for B16-F10 cells), and McCoy's 5A medium supplemented with 10% FCS, benzylpenicillin (100 u/ml) and streptomycin (100 μg/ml) for HCT-116 cells.

Toxicity

In vitro cytotoxicity of pradimicin A was determined against various cultured mammalian cells. As shown in Table 10, pradimicin A was not cytotoxic against all cells tested at 100 or 500 μg/ml. The LD_{50} values in mice were 120 and more than 400 mg/kg by iv and im administrations, respectively. Transient body weight loss was observed in the mice injected at higher doses than 20 and 50 mg/kg by iv and im administrations, respectively.

Antiviral Activity

In vitro antiviral activity of pradimicin A was determined against influenza and herpes simplex viruses by the plaque reduction assay. As shown in Table 11, pradimicin A potently inhibited replication of influenza virus with an IC_{50} value of 6.8 μg/ml without cytotoxic activity against host MDCK cells at 200 μg/ml.

Discussion

Pradimicins A, B and C are novel antifungal antibiotics produced by *A. hibisca* No. P157-2 (ATCC 53557)[1~7]. They showed potent *in vitro* antifungal activity and broad antifungal spectrum against a wide variety of fungi and yeasts. Antibacterial activity of pradimicin A was seen against only *Micrococcus luteus* with a MIC value of 3.1 μg/ml[1~3]. The *in vitro* results suggested their broad therapeutic efficacy in systemic fungal infections, though their *in vitro* potencies were significantly less than that of amphotericin B. In fact, pradimicins A, B and C all exhibited significant protection in the systemic infection with *C. albicans* A9540, which is sensitive to various types of antifungal agents, at similar dose levels by either single iv (PD_{50} = 7.9 ~ 14 mg/kg) or bid × 2 im (PD_{50} = 16 ~ 21 mg/kg/dose) administration. Pradimicin A was also significantly effective on the systemic infections with azole- or 5-fluorocytosine-resistant *C. albicans*, *A. fumigatus* IAM 2034 and *C. neoformans* IAM 4514 by the same treatment conditions as above. In immunocompromized mice, pradimicin A was active against systemic infections with *C. tropicalis* CS-07

Table 11. *In vitro* antiviral activity of pradimicin A by the plaque reduction assay.

Compound	Influenza A virus		Herpes simplex virus	
	IC_{50} (μg/ml)	TC_{50} (μg/ml)	IC_{50} (μg/ml)	TC_{50} (μg/ml)
Pradimicin A	6.8	>200	>200	>200
Ribavirin	1.6	>200	ND	ND
Acyclovir	ND	ND	0.02	>200

IC_{50}: 50% inhibitory concentration to viral replication.
TC_{50}: 50% cytotoxic concentration to host cells.
ND: Not done.

as well as the above three pathogens. Pradimicin A was 2~4 times less active against *C. albicans*, *C. neoformans* or *A. fumigatus* in immunocompromized mice than in normal mice by a single iv administration in terms of PD_{50} values, but its anti-*Candida* activity was equivalent in immunocompromized and normal mice with bid×2 im treatment. As described above, pradimicin A showed excellent *in vivo* antifungal activity against various systemic fungal infections in both normal and immunocompromized animals. Since, most deep fungal infections are known to be caused by species of *Candida*, *Aspergillus* and *Cryptococcus neoformans* particularly frequently in immunocompromized patients having cancer, AIDS *etc.*, the above results strongly suggest the clinical usefulness of pradimicin A against a variety of systemic fungal infections.

In the experimental lung infection with *C. albicans* or *A. fumigatus*, and the vaginal infection with *C. albicans*, pradimicin A showed significant therapeutic efficacy by iv administration. Furthermore, the antibiotic inhibited both vaginal and skin infections with *C. albicans* and *T. mentagrophytes*, respectively, with topical application. In vaginal candidiasis, the EC_{50} value of pradimicin A was 0.33%, which is a clinically applicable concentration.

Pradimicin A was not cytotoxic to various cultured mammalian cells at 10 to 100 times higher concentrations (100~500 μg/ml) than the antifungal MIC values (0.8~12.5 μg/ml). In the acute toxicity experiments in mice, the LD_{50} values were 120 and more than 400 mg/kg by iv and im administrations, respectively. Pradimicin A was found to possess a Ca^{++}-dependent binding capability to yeast cell surfaces but not to mammalian cell membranes[9]. These results suggest that the specific binding to fungal cell surfaces plays, in part, a role in the selective toxicity of pradimicin A against fungal cells. The antibiotic had no mutagenic potential in the Ames test and the *E. coli* reverse mutation assay (unpublished data).

In addition to the antifungal activity, pradimicin A inhibited influenza virus replication in MDCK cells with an IC_{50} value of 6.8 μg/ml without cytotoxicity at 200 μg/ml. Recently YAMAMOTO *et al.*[10] reported that pradimicin A suppressed the cell damage induced by HIV at concentrations more than 3.5 μg/ml and suggested its anti-HIV effects on the stage of viral adsorption and cell to cell infection. Taking into consideration the serious systemic fungal infections in AIDS patients, it would be worthwhile to study pradimicin A in the treatment of AIDS patients.

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