STUDIES ON PENEM ANTIBIOTICS

II. *IN VITRO* ACTIVITY OF SUN5555, A NEW ORAL PENEM

TAKESHI NISHINO, YOKO MAEDA†, EMIKO OHTSU and SATOYO KOIZUKA

Department of Microbiology, Kyoto Pharmaceutical University,
Misasagi, Yamashina, Kyoto 607, Japan

TATSURO NISHIHARA, HIDEKI ADACHI, KIYOMI OKAMOTO
and MASAJI ISHIGURO*

Suntory Institute for Biomedical Research,
Shimamoto, Mishima, Osaka 618, Japan

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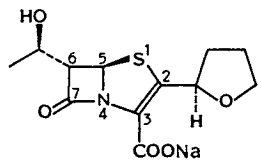
The new oral penem antibiotic SUN5555 shows broad antibacterial activity against both aerobic and anaerobic Gram-positive and Gram-negative bacteria. SUN5555 is highly stable against various β-lactamases. It binds preferentially to the penicillin-binding proteins 2 and 1A of *Escherichia coli*.

Although community-acquired pathogens have historically been susceptible to current oral agents, resistant and multiple-resistant isolates are becoming increasingly prevalent. The clinical utility of the oral β-lactam antibiotics such as oral penicillins and cephalosporins is being rapidly eroded by the increasing clinical isolation of β-lactamase-producing strains, due to the acquisition and transfer of plasmid-mediated determinants[1,2]. The emergence of isolates of methicillin-resistant *Staphylococcus aureus* imposes a serious limitation on the use of newer oral cephalosporins. Penem antibiotics possess the β-lactam ring and show broad and potent antibacterial activity against both aerobic and anaerobic Gram-positive and Gram-negative bacteria including β-lactamase-producing strains. Although as yet only a few penems have been submitted to broad preclinical and clinical investigations, there is great interest in exploiting modifications of these compounds. Herein we report the *in vitro* antibacterial activity of a new penem, SUN5555 (sodium (5*R*,6*S*,8*R*,2′*R*)-2-(2′-tetrahydrofuryl)-6-hydroxyethylpenem-3-carboxylate, Fig. 1)[3].

Fig. 1. Chemical structure of SUN5555.



Materials and Methods

Bacteria

The bacterial strains used were clinical isolates collected from various hospitals in Japan and laboratory strains. All bacteria strains were stored in Nutrient Broth (Nissui Pharmaceutical Co., Ltd., Tokyo) containing 10% skim-milk at −80°C and then were maintained on Casitone Semisolid Agar (Eiken, Tokyo) or on Nutrient Agar (Nissui) with proper supplements for aerobes until used. Anaerobes were maintained in GAM Agar (Nissui).

† On leave from Suntory Institute for Biomedical Research.

Antibiotics

SUN5555 was synthesized and purified in Suntory Institute for Biomedical Research, Osaka, Japan. Cefteram pivoxil, a prodrug formulation of cefteram, was kindly supplied from Toyama Chemical Co., Ltd., Tokyo, Japan; cefixime was from Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan; cefaclor was from Shionogi & Co., Ltd., Osaka, Japan; and other antibiotics were purchased from commercial sources.

Susceptibility Testing

Comparative MICs were determined by the 2-fold agar dilution method. Heart Infusion Agar (Nissui) or Sensitivity Disk Agar-N (modified Mueller-Hinton agar, Nissui) was used for the susceptibility testing of aerobic bacteria except for *Branhamella catarrhalis*, for which Chocolate agar containing 5% defibrinated horse blood (Nippon Bio-Test Laboratories Inc., Japan) was used, and for *Neisseria gonorrhoeae* and *Neisseria meningitidis* for which GC Agar (Eiken) was used. GAM Agar (Nissui) was used for anaerobes. Media were supplemented with 10% of defibrinated horse blood for the testing of *Streptococcus* and *Enterococcus* sp. and 3% Fildes enrichment (Difco Laboratories, Detroit, U.S.A.) for *Haemophilus influenzae*. Inocula were prepared by diluting overnight broth cultures (Sensitivity test broth or Trypto-Soya Broth, (Nissui) with proper supplements) to *ca.* 10^6 cfu/ml. Plates were inoculated with an inoculator delivering 2 μl resulting in a test inoculum of 2×10^3 cfu. Plates were incubated for 18 hours at 37°C in air, at 37°C in 5% CO_2 or at 35°C anaerobically (Forma Scientific, Marietta, U.S.A.). The MICs for 50 and 90% of isolates (MIC_{50} and MIC_{90}, respectively) were calculated from the cumulative percent inhibition curves.

Influence of Inoculum Size

The influence of the inoculum size on the activity of SUN5555 was examined by the 2-fold agar dilution method using Heart Infusion Agar. Inocula were approximately 1×10^5, 10^6, 10^7 and 10^8 cfu/ml of Trypto - Soya Broth medium.

Influence of the pH of Culture Medium

The effect of the pH of the culture media on the activity of SUN5555 was studied in Heart Infusion Agar which had been adjusted to values of pH 5.5, 7.0 and 8.5. The MICs of SUN5555 for 10^6 cfu/ml of the test strains were determined by the 2-fold agar dilution method.

Killing Curves

The kinetics of bactericidal activity was determined for the selected test strains. An overnight broth culture was diluted into Heart Infusion Broth (Nissui) containing the indicated concentrations of the antibiotic, and cultures were incubated at 37°C with shaking. Samples of 0.1 ml were withdrawn at the times indicated, diluted with buffer and spread on antibiotic-free agar plates. The initial counts were approximately 10^6 cfu/ml and after 18 hours at 37°C the number of cfu/ml on each plate was counted.

The resistance to β-lactamase of each of RGN 823, Rms 213 and RGN 238 was introduced to *Escherichia coli* KC-14 by transconjugation[4].

β-Lactamase Stability

The enzymes used were prepared by ultracentrifugation of bacterial cell extracts obtained by ultrasonication of cell suspension. The β-lactamase activity was determined by a spectrometric method[5] using a 0.1-mM concentration of each antibiotic and was expressed in relative rate of hydrolysis, taking the rate of benzylpenicillin for penicillinases or that of cephaloridine for cephalosporinases as 100.

Affinity for Penicillin-binding Proteins (PBPs)

The binding of SUN5555 to PBPs of *E. coli* NIH JC-2 was determined by competition with [^{14}C]-benzylpenicillin as described[6]. Washed cell envelopes of *E. coli* were preincubated with a range of SUN5555 concentrations for 10 minutes at 30°C, and the binding proteins remaining accessible to benzylpenicillin were detected by the addition of a saturating concentration of [^{14}C]benzylpenicillin. After another 10 minutes incubation at 30°C, the binding proteins were separated on sodium dodecyl-

sulfate - polyacrylamide slab gels after solubilization of the inner membranes with Sarkosyl NL-97 and quantitated by densitometry of the X-ray films.

Abbreviations

Abbreviations used in Tables and Figs. are: CCL, cefaclor; CFIX, cefixime; CFTM, cefteram; AMPC, amoxicillin; Pc-G, benzylpenicillin; CER, cephaloridine; CFX, cefoxitin; CTX, cefotaxime.

Results

The Inhibitory Activity *In Vitro*

The inhibitory activity *in vitro* of SUN5555 compared with four other oral antibacterial agents is shown in Tables 1 through 3 (against aerobic and facultative anaerobic bacteria) and Table 4 (against obligate anaerobes). SUN5555 possesses a broad antibacterial spectrum, which includes both Staphylococci and Streptococci. The *in vitro* activity of SUN5555 against *S. aureus* is clearly superior to all reference compounds. Sixty-seven % of 43 methicillin-resistant *S. aureus* strains are susceptible to SUN5555 with MIC value below 3.13 μg/ml. Against clinical isolates of Enterococci, SUN5555 exhibits excellent activity, similar to that of imipenem (MIC_{50}: *Enterococcus faecalis* (30 strains) 0.78 μg/ml, *Enterococcus faecium* (29 strains) 6.25 μg/ml, *Enterococcus avium* (14 strains) 3.13 μg/ml).

Members of the Enterobacteriaceae, *Neisseria* species, *H. influenzae* and *B. catarrhalis* are susceptible to SUN5555 and 90% of these strains are inhibited at concentrations below 1.0 μg/ml. Strains of indole-negative and indole-positive *Proteus* species are inhibited at therapeutic concentrations. SUN5555 is not active against *Pseudomonas aeruginosa* and exhibits varying activity against strains of *Serratia marcescens*. Of the compounds examined, SUN5555 is the most active against all strains

Table 1. *In vitro* antimicrobial activity of SUN5555 and other β-lactam antibiotics against Gram-positive bacteria.

Organism	MIC (μg/ml)				
	SUN5555	CCL	CFIX	CFTM	AMPC
Staphylococcus aureus 209P JC-1	0.1	0.78	100	3.13	0.1
S. aureus Smith	0.1	0.78	50	3.13	0.1
S. aureus Terajima	0.2	6.25	50	6.25	0.78
S. aureus E-46	0.1	0.78	25	3.13	0.1
S. aureus Neumann	0.2	1.56	50	3.13	0.2
S. aureus No. 80 (Pc-R)	0.1	1.56	25	3.13	1.56
S. epidermidis	0.78	1.56	100	12.5	0.39
Streptococcus pyogenes S-23	<0.025	0.2	0.2	<0.025	<0.025
S. pyogenes Cook	0.05	0.39	0.2	<0.025	0.05
S. pyogenes C-203	<0.025	0.2	0.1	<0.025	<0.025
Viridans *Streptococcus*	12.5	100	>100	>100	1.56
Enterococcus faecalis	6.25	100	>100	>100	1.56
Streptococcus pneumoniae Type I	<0.025	1.56	0.2	<0.025	<0.025
S. pneumoniae Type II	<0.025	0.78	0.2	<0.025	<0.025
S. pneumoniae Type III	<0.025	0.78	0.2	<0.025	<0.025
Corynebacterium diphtheriae	0.78	0.78	25	3.13	0.78
C. diphtheriae Toronto	0.1	0.05	1.56	0.2	0.05
Micrococcus luteus ATCC 9341	0.1	<0.025	3.13	<0.025	<0.025
Bacillus subtilis ATCC 6633	<0.025	0.05	3.13	0.2	<0.025
B. anthracis	<0.025	0.39	>100	6.25	<0.025

Table 2. *In vitro* antimicrobial activity of SUN5555 and other β-lactam antibiotics against Gram-negative bacteria.

Organism	MIC (μg/ml)				
	SUN5555	CCL	CFIX	CFTM	AMPC
Neisseria gonorrhoeae	<0.025	0.05	<0.025		0.1
N. meningitidis	<0.025	0.39	<0.025		0.05
Escherichia coli NIHJ JC-2	1.56	3.13	1.56	0.78	12.5
E. coli NIHJ	0.2	1.56	0.78	0.05	6.25
E. coli K-12	0.78	0.78	0.39	0.2	3.13
Citrobacter freundii NIH 10018-68	0.78	>100	25	1.56	>100
Salmonella typhi T-287	0.1	0.2	0.05	<0.025	0.2
S. typhi O-901	0.2	0.39	<0.025	0.05	0.39
S. paratyphi A	0.39	1.56	0.05	0.05	0.39
S. paratyphi B	0.2	0.78	0.1	0.1	0.78
S. enteritidis	0.39	0.39	0.1	0.05	0.39
Shigella dysenteriae EW-7	0.78	1.56	0.78	0.2	3.13
S. flexneri 2a EW-10	0.39	0.78	0.78	0.05	3.13
S. boydii EW-28	0.78	0.78	0.78	0.05	6.25
S. sonnei EW-33	0.39	0.78	0.78	0.05	3.13
Klebsiella pneumoniae KC-1	0.78	0.78	0.19	0.39	1.56
K. pneumoniae NCTC 9632	0.78	0.78	0.1	0.2	50
Enterobacter cloacae NCTC 9394	3.13	>100	12.5	0.78	>100
E. aerogenes NCTC 10006	3.13	>100	12.5	0.78	>100
Hafnia alvei NCTC 9540	1.56	>100	3.13	1.56	100
Serratia marcescens IFO 3736	12.5	>100	0.78	3.13	100
S. marcescens T-55	12.5	>100	3.13	3.13	50
Proteus vulgaris OX-19	0.39	25	0.05	<0.025	100
P. mirabilis 1287	1.56	6.25	<0.025	<0.025	0.78
Morganella morganii Kono	1.56	>100	6.25	0.2	>100
Providencia rettgeri NIH 96	0.78	0.78	<0.025	<0.025	0.39
P. inconstans NIH 118	0.78	6.25	<0.025	0.05	100
Pseudomonas aeruginosa E-2	>100	>100	>100	>100	>100
P. aeruginosa NCTC 10490	25	>100	25	50	>100
P. aeruginosa PAO 1	>100	>100	100	100	>100
Xanthomonas maltophilia ATCC 13637	>100	>100	>100	>100	>100
Acinetobacter calcoaceticus AC-54	12.5	50	50	50	25
A. calcoaceticus AC-86	3.13	50	25	12.5	12.5

of anaerobic bacteria tested. The highest MIC determined for some *Bacteroides* sp. is 0.78 μg/ml. The minimum difference between the values of MIC_{50} and MIC_{90} of SUN5555 against various test organisms indicates that the activity is little affected by β-lactamases or other resistance determinants.

Influence of the Inoculum Size on the MIC

The MICs of SUN5555 against each of *S. aureus*, *E. coli* and *Klebsiella pneumoniae* were determined with different inoculum sizes. The resulting cumulative percent inhibition curves are shown in Fig. 2. The inoculum size has little or no effect on the *in vitro* activity of SUN5555 against *S. aureus* with all sizes of inocula examined. The activity is little affected up to the inocula of 10^6 and 10^7 cfu/ml against *E. coli* and *K. pneumoniae*, respectively. The activity of SUN5555 is less affected by the inoculum sizes tested when compared to cefaclor.

Effect of the pH of Culture Medium on the MIC

From Fig. 3, the MICs of SUN5555 determined between pH 5.5 and 8.5 varied over one to three

Table 3. Antibacterial activity of SUN5555 and reference compounds against clinical isolates.

Organism (No. of strains)	Antibiotic	μg/ml		
		MIC range	MIC_{50}	MIC_{90}
Staphylococcus aureus (87)	SUN5555	<0.025~0.2	0.1	0.2
	CFTM	0.78~6.25	3.13	3.13
	CFIX	3.13~25	12.5	12.5
	CCL	<0.025~6.25	1.56	3.13
	AMPC	<0.025~3.13	0.2	1.56
Methicillin-resistant *S. aureus* (43)	SUN5555	0.39~100	1.56	>100
	Methicillin	3.13~>100	50	>100
	CFTM	12.5~>100	>100	>100
	CFIX	>100	>100	>100
	AMPC	25~100	50	100
Streptococcus pyogenes (37)	SUN5555	<0.025~0.05	<0.025	0.05
	CFTM	<0.025	<0.025	<0.025
	CFIX	0.1~0.39	0.2	0.2
	CCL	0.1~1.56	0.2	0.39
	AMPC	<0.025~0.05	<0.025	0.05
Escherichia coli (88)	SUN5555	0.1~3.13	0.78	1.56
	CFTM	<0.025~6.25	0.2	0.78
	CFIX	0.1~>100	0.39	1.56
	CCL	0.78~>100	3.13	6.25
	AMPC	0.2~>100	6.25	>100
Klebsiella sp. (63)	SUN5555	0.39~6.25	0.78	1.56
	CFTM	<0.025~25	0.39	0.39
	CFIX	<0.025~>100	0.1	0.1
	CCL	0.39~>100	0.78	6.25
	AMPC	1.56~>100	>100	>100
Proteus mirabilis (30)	SUN5555	0.78~6.25	3.13	6.25
	CFTM	<0.025~0.39	0.1	0.2
	CFIX	<0.025	<0.025	<0.025
	CCL	0.78~6.25	1.56	3.13
	AMPC	0.39~6.25	0.78	1.56
P. vulgaris (41)	SUN5555	0.39~25	3.13	6.25
	CFTM	<0.025~25	0.2	0.78
	CFIX	<0.025~1.56	<0.025	0.1
	CCL	1.56~>100	>100	>100
	AMPC	0.78~>100	6.25	>100
Morganella morganii (29)	SUN5555	0.39~12.5	1.56	12.5
	CFTM	0.1~25	0.2	12.5
	CFIX	0.05~50	0.78	50
	CCL	50~>100	>100	>100
	AMPC	50~>100	>100	>100
Providencia rettgeri (17)	SUN5555	0.78~6.25	3.13	6.25
	CFTM	<0.025~12.5	0.78	6.25
	CFIX	<0.025~0.78	0.1	0.78
	CCL	1.56~>100	>100	>100
	AMPC	0.78~25	6.25	25
Serratia marcescens (88)	SUN5555	3.13~100	12.5	50
	CFTM	0.39~>100	6.25	100
	CFIX	0.2~>100	1.56	25
	CCL	>100	>100	>100
	AMPC	25~>100	>100	>100
Haemophilus influenzae (25)	SUN5555	0.05~1.56	0.39	1.56
	CFIX	<0.025~0.78	0.025	0.39
	CCL	0.1~50	0.78	25
	AMPC	0.1~12.5	0.39	6.25

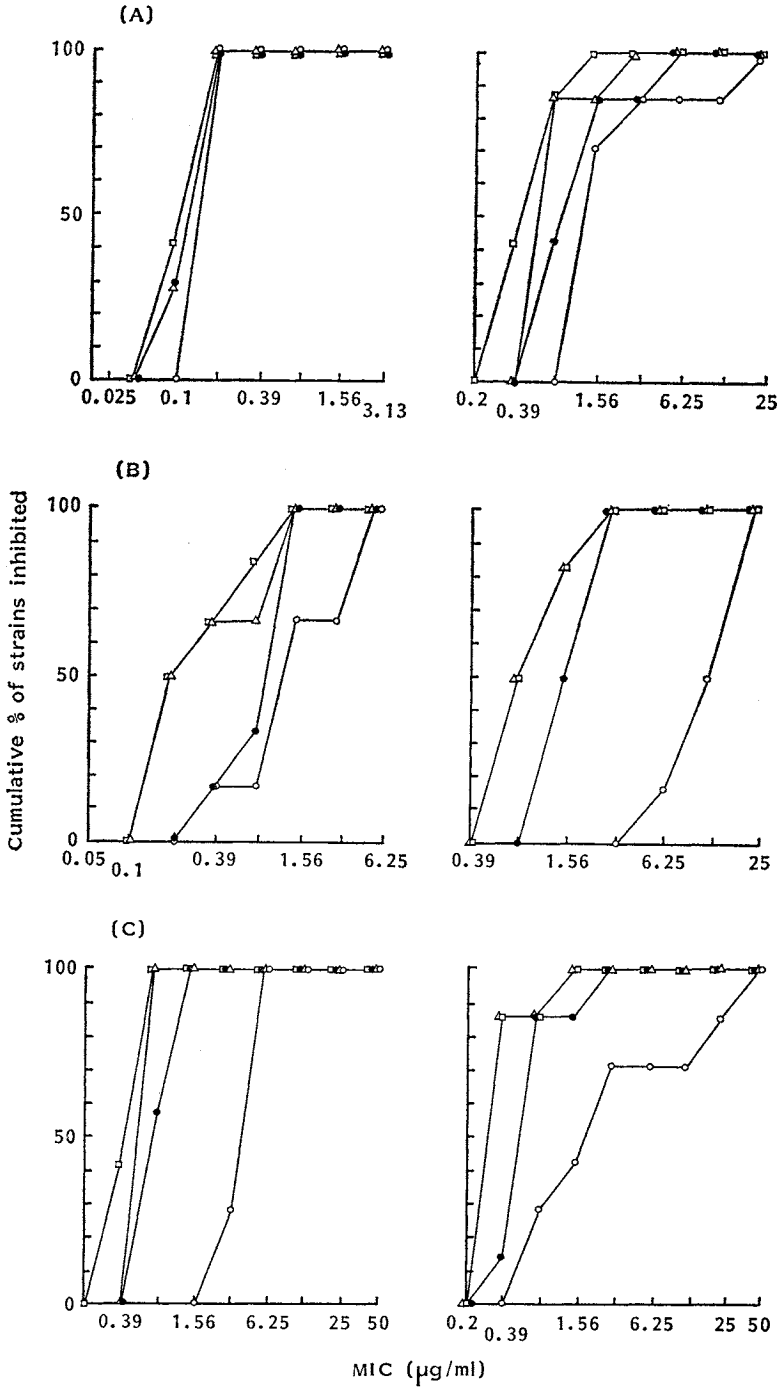
Table 3. (Continued)

Organism (No. of strains)	Antibiotic	μg/ml		
		MIC range	MIC_{50}	MIC_{90}
Branhamella catarrhalis (18)	SUN5555	0.05~0.78	0.39	0.78
	CFTM	0.1~1.56	0.78	1.56
	CFIX	0.05~1.56	0.2	0.39
	CCL	0.39~1.56	0.39	0.78
	AMPC	0.05~6.25	1.56	6.25
Enterobacter aerogenes (34)	SUN5555	0.78~25	6.25	12.5
	CFTM	0.2~>100	0.78	50
	CFIX	0.2~>100	1.56	>100
	CCL	25~>100	100	>100
	AMPC	>100	>100	>100
E. cloacae (29)	SUN5555	1.56~25	6.25	12.5
	CFTM	0.2~25	0.78	3.13
	CFIX	0.05~100	1.56	12.5
	CCL	0.78~>100	100	>100
	AMPC	>100	>100	>100
Acinetobacter calcoaceticus (57)	SUN5555	0.2~25	6.25	25
	CFTM	0.39~>100	25	>100
	CFIX	0.78~>100	12.5	100
	CCL	1.56~>100	50	>100
	AMPC	3.13~>100	25	50

Table 4. *In vitro* antimicrobial activity of SUN5555 and β-lactam antibiotics against anaerobes.

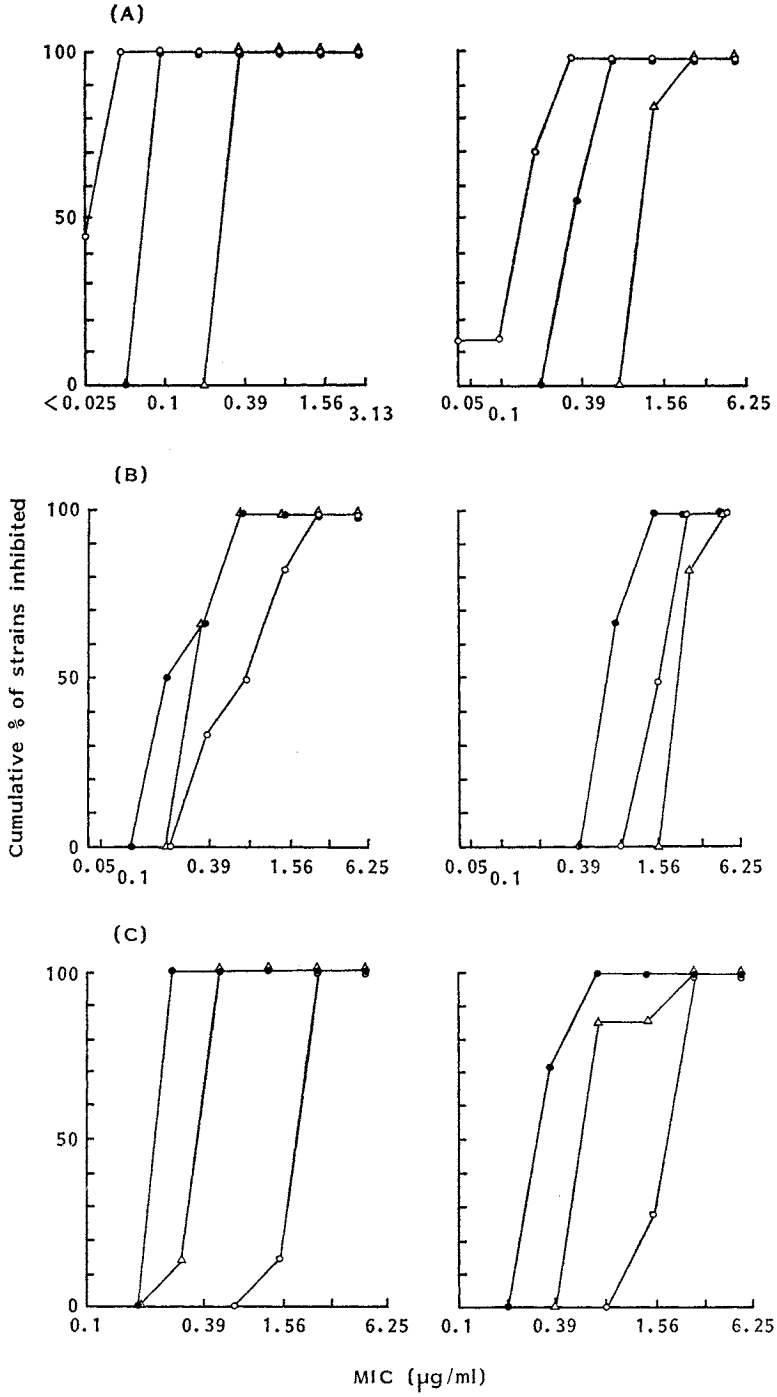
Organism	MIC (μg/ml)				
	SUN5555	CCL	CFIX	CFTM	AMPC
Clostridium tetani	0.05	0.78	1.56	0.78	0.1
C. perfringens	0.39	0.39	25	12.5	0.2
C. sporogenes GAI 0005	0.2	1.56	12.5	12.5	0.2
Bacteroides fragilis GM 7000	<0.025	>100	6.25	6.25	12.5
B. fragilis V-283	0.1	>100	100	100	>100
B. fragilis ATCC 25285	<0.025	>100	25	6.25	12.5
B. fragilis R-1-23	<0.025	>100	25	12.5	12.5
B. fragilis R-2-8	<0.025	>100	25	12.5	12.5
B. fragilis V-224-1	0.78	>100	>100	>100	>100
B. fragilis V-240-2	0.2	>100	100	>100	>100
B. fragilis V-271-1	0.39	>100	100	>100	100
B. fragilis V-280-1	<0.025	>100	12.5	3.13	6.25
B. fragilis V-288	0.1	>100	>100	>100	50
B. fragilis V-307-2	0.1	>100	>100	>100	>100
B. thetaiotaomicron 5600	0.2	>100	>100	>100	>100
B. thetaiotaomicron WAL 2926	0.1	>100	25	25	12.5
B. thetaiotaomicron WAL 3304	0.2	>100	25	25	12.5
B. distasonis Ju-11-1	<0.025	100	3.13	6.25	6.25
B. distasonis clin-99-3	0.78	>100	6.25	25	50
B. vulgatus ES-14	0.2	100	1.56	6.25	12.5
B. vulgatus ES-21	0.1	100	1.56	6.25	12.5
B. ovatus Ju-6-1	0.39	>100	25	25	25
Fusobacterium varium ATCC 8501	0.2	100	3.13	12.5	1.56
F. varium B-1083	0.2	50	0.78	3.13	12.5
F. varium 1482	0.2	25	3.13	12.5	0.78
F. mortiferum F-1-9	0.2	12.5	1.56	3.13	0.78

Fig. 2. Effect of inoculum size on antimicrobial activity.



The MICs of SUN5555 (left) and CCL (right) against each of four different inoculum sizes (○ 10^8 cfu/ml, ● 10^7 cfu/ml, △ 10^6 cfu/ml, □ 10^5 cfu/ml) of *Staphylococcus aureus* (7 isolates) (A), *Escherichia coli* (6 isolates) (B) and *Klebsiella pneumoniae* (7 isolates) (C) are expressed as cumulative percent inhibition curves.

Fig. 3. Effect of medium pH on antimicrobial activity.



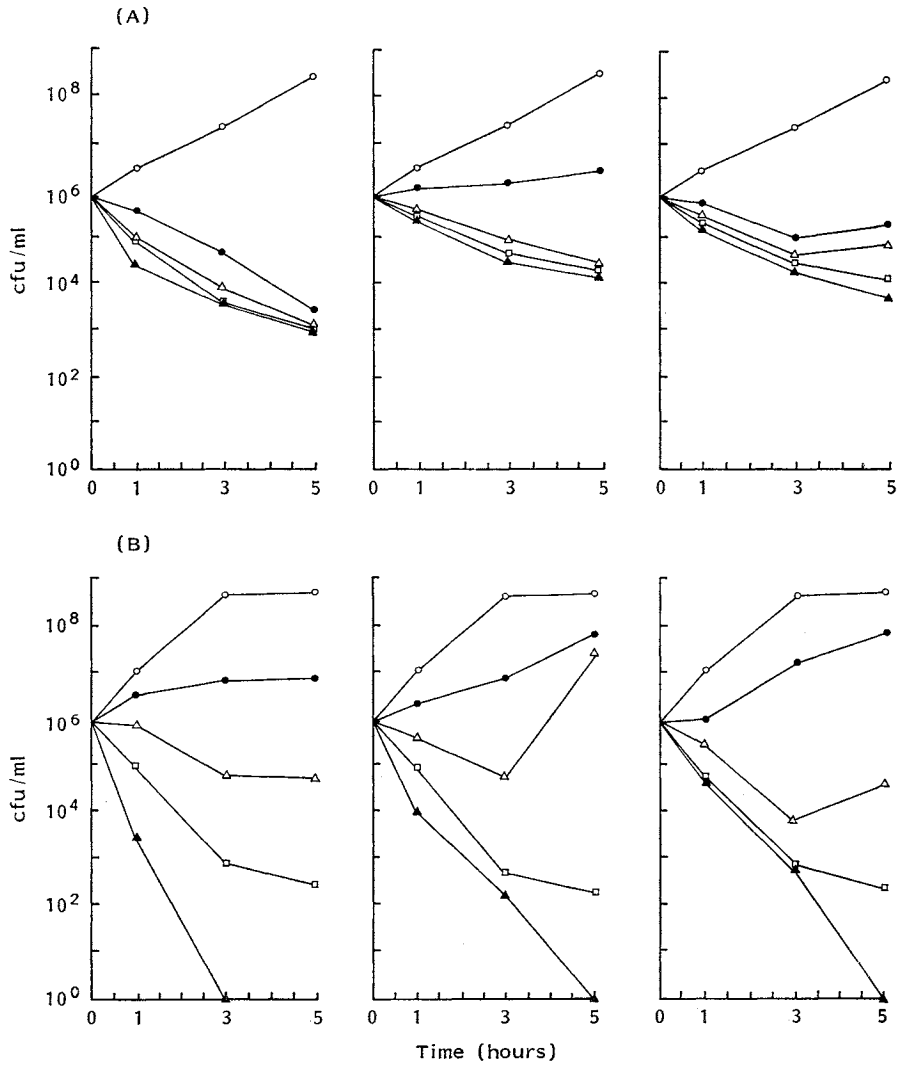
The MICs of SUN5555 (left) and CCL (right) against each of *Staphylococcus aureus* (7 isolates) (A), *Escherichia coli* (6 isolates) (B) and *Klebsiella pneumoniae* (7 isolates) (C) at three different pHs of the culture media (○ pH 5.5, ● pH 7.0, △ pH 8.5) are expressed as cumulative percent inhibition curves.

dilution steps and the profiles were comparable to that of cefaclor.

Bactericidal Activity

Fig. 4 shows the bactericidal activity of SUN5555 compared to other oral β-lactams against various test organisms. The slopes of the curves in Fig. 4 demonstrate that the number of surviving *S. aureus* cells decreases steadily after the addition of SUN5555 in concentrations corresponding as low as 1/4 MIC. With *E. coli*, the addition of SUN5555 at once and twice the MIC caused sharp decrease in the number of cfu in the culture. The slopes of the killing curves obtained with these concentrations of SUN5555 were comparable to those of cefixime and cefteram.

Fig. 4. Bactericidal activities of SUN5555, CFIX and CFTM.



Cultures of 10^6 cfu/ml of *Staphylococcus aureus* 209P (A) and *Escherichia coli* NIHJ JC-2 (B) were incubated in the absence (○ control) and the presence (● 1/4 MIC, △ 1/2 MIC, □ MIC, ▲ 2-fold MIC) of the antibiotics of SUN5555 (left), CFIX (middle) and CFTM at (right) 37°C. Each point represents the number of colonies at the time indicated.

Table 5. Stability of SUN5555 to β-lactamase.

β-Lactamase	Organism	Relative rate of hydrolysis							
		SUN5555	Pc-G	AMPC	CER	CCL	CFIX	CFX	CTX
Penicillinase	*Klebsiella pneumoniae* 130 (type I)[a]	<0.1	100	60	12	3	<0.1	<0.1	NT
	Escherichia coli 195 (type II)[a]	<0.1	100	435	16	16	<0.1	<0.1	0.1
	E. coli 113 (type III)[a]	<0.1	100	58	19	4	<1	<0.1	0.1
	K. pneumoniae 102 (type IV)[a]	<0.1	100	155	15	4	<0.1	<0.1	NT
	Staphylococcus aureus S-54 (type V)[a]	<0.1	100	300	NT	NT	NT	NT	NT
Cephalosporinase	*E. coli* 106	<0.1	197	<1	100	256	<0.1	<0.1	NT
	Morganella morganii 111	<0.1	408	38	100	436	828	<0.1	NT
	Providencia rettgeri 105	<0.1	5	6	100	64	1	<0.1	NT
	Pseudomonas aeruginosa E-2	<0.1	142	28	100	100	<1	<1	<1
	Enterobacter cloacae 45	<0.1	7	<0.1	100	61	<1	<0.1	0.1
Cefuroximase	*Bacteroides fragilis* V240-2	<0.1	17	<0.1	100	51	17	<1	53

[a] Mitsuhashi classification.

Table 6. Affinity of SUN5555 for penicillin-binding proteins of *Eschericiha coli* NIHJ JC-2.

Drug	MIC (μg/ml)	ID_{50} (μg/ml)						
		1A	1Bs	2	3	4	5	6
SUN5555	0.78	0.3	7.5	<0.1	17.8	0.2	2.3	19.7

Values indicate the concentration of SUN5555 required to reduce [^{14}C]benzylpenicillin binding by 50%.

The bactericidal activity of SUN5555 is virtually indifferent to the genetic introduction of β-lactamase to a test organism in contrast to that of amoxicillin[7].

β-Lactamase Stability

Table 5 shows the relative rates of hydrolysis of SUN5555 and other β-lactams by β-lactamases from various sources. The data indicate that SUN5555 is extremely stable against all the plasmid-mediated and chromosomally mediated β-lactamases tested. The stability of SUN5555 against hydrolysis by β-lactamases is equivalent to that of cefoxitin and no significant hydrolysis of SUN5555 occurs with the chromosomally coded enzyme prepared from *Bacteroides fragilis* V240-2 which rapidly hydrolyzes cefotaxime.

Affinity for PBPs

As shown in Table 6, SUN5555 binds preferentially to the PBP2 and 1A of *E. coli* inner membrane. These observations are consistent with the morphological effects of SUN5555 on *E. coli*. SUN5555 causes the spheroplast and bulge formation at sub-MIC concentrations and leads to bacteriolysis at the MIC or above.

Discussion

SUN5555 is a novel oral synthetic penem. In contrast to cephalosporins and penicillins, the penem antibiotics have shown a unique antibacterial spectrum which includes anaerobic bacteria as well as Gram-positive and most Gram-negative pathogens[8~12]. These properties can also be found with the new penem SUN5555. Although it lacks the activity against *Pseudomonas* species, SUN5555 is much more potent against members of *Staphylococcus* and *Streptococcus* as well as most of Gram-negative organisms including *H. influenzae*, *N. gonorrhoeae* and *B. catarrhalis* than the reference oral β-lactams, cefteram, cefixime, cefaclor and amoxicillin. SUN5555 is equally active against organisms carrying the common plasmid-mediated and chromosomally mediated β-lactamases. However, slightly higher MICs of SUN5555 have been determined for *Proteus* species than those of cefteram and cefixime, which nevertheless should allow successful therapy of infections caused by these pathogens. The activity *in vitro* of SUN5555 extends to some of the methicillin-resistant strains of *S. aureus*. In contrast to other β-lactams, SUN5555 also exhibits marked activity against Gram-positive and Gram-negative anaerobic bacteria partly because of its stability against β-lactamase and partly because of its intrinsic activity. A noteworthy feature of SUN5555 is the narrow range of MIC values for the susceptibility of organisms in contrast to the marked wide range of susceptibility to the newer oral cephalosporins. SUN5555 could therefore be said to possess a predictable degree of antimicrobial activity against a wide range of pathogens. Since high peak levels of serum are obtained after oral administrations to mice, rabbits and dogs[13] and initial results also show good chemotherapeutic activity in experimental infections, it appears that SUN5555 has a remarkable potential for oral treatment of infectious diseases that are less predictably treatable with the currently available oral agents. As a role for SUN5555 as an outpatient adjunct to primary parenteral therapy can be envisaged, it would be worthwhile to continue the evaluation of SUN5555.

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