ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1999, p. 454–459 Vol. 43, No. 3
0066-4804/99/$04.00+0

In Vitro Activities of Aminomethyl-Substituted Analogs of Novel Tetrahydrofuranyl Carbapenems

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Received 24 April 1998/Returned for modification 18 September 1998/Accepted 9 December 1998

CL 188,624, CL 190,294, and CL 191,121 are novel aminomethyl tetrahydrofuranyl (THF)-1β-methylcarbapenems. The in vitro antibacterial activities of these THF carbapenems were evaluated and compared with those of biapenem, imipenem, and meropenem against 554 recent clinical isolates obtained from geographically distinct medical centers across North America. The antibacterial activities of the THF carbapenems were equivalent to that of biapenem, and the THF carbapenems were slightly more active than imipenem and less active than meropenem against most of the members of the family *Enterobacteriaceae* but lacked significant activity against *Pseudomonas* isolates. In general, CL 191,121 was two- to fourfold more active than CL 188,624 and CL 190,294 against the staphylococcal and enterococcal isolates tested. CL 191,121 was twofold less active than imipenem against methicillin-susceptible staphylococci and was as activity as imipenem against *Enterococcus faecalis* isolates. Biapenem and meropenem were two- and fourfold less active than CL 191,121, respectively, against the methicillin-susceptible staphylococci and *E. faecalis*. All the carbapenems displayed equivalent good activities against the streptococci. Biapenem was slightly more active than the other carbapenems against *Bacteroides fragilis* isolates. Time-kill curve studies demonstrated that the THF carbapenems were bactericidal in 6 h against *Escherichia coli* and *Staphylococcus aureus* isolates. The postantibiotic effect exerted by CL 191,121 was comparable to or slightly longer than that of imipenem against isolates of *S. aureus*, *E. coli*, and *Klebsiella pneumoniae*.

Carbapenem antibiotics have extremely potent activities against a wide range of aerobic and anaerobic gram-positive and gram-negative bacteria (9, 13, 21, 22). These activities are due to stability to hydrolysis by most β-lactamases, a high affinity for essential penicillin-binding proteins, and penetrability into most gram-negative organisms (4, 14, 28). The addition of the 1β-methyl group is responsible for the high degree of chemical stability as well as stability to renal dehydropeptidase, thereby eliminating the requirement, as with imipenem, for coadministration with cilastatin, a dehydropeptidase inhibitor, for in vivo efficacy (6). Meropenem, which was recently approved for use, contains this 1β-methyl group and also exhibits excellent activity, especially against gram-negative bacterial isolates, as do several investigational carbapenems (3, 7). As part of a carbapenem discovery program, novel 1β-methylcarbapenems with structural modification at the 2 position on the carbapenem molecule have been synthesized (12). Among them, a series of [aminomethyl(3-tetrahydrofuranylthio)]-1β-methylcarbapenems (tetrahydrofuranyl [THF] carbapenems) proved to be the most active (11). This study was performed to evaluate the in vitro activities of CL 191,121 (the 3*R*,2*R* diastereomer), CL 188,624 (a mixture of the 3*R*,5*S* and the 3*S*,5*R* diastereomers), and CL 190,294 (a mixture of the 3*R*,5*R* and the 3*S*,5*S* diastereomers) (Fig. 1) against a broad range of clinical isolates.

MATERIALS AND METHODS

Organisms. The 554 organisms (356 gram-negative and 174 gram-positive aerobes and 24 anaerobes) used for this study represent recent clinical isolates (1987 to 1993) from various medical centers and hospital outbreaks referred to the Antimicrobial Chemotherapy laboratory. The identification of the organisms in the cultures was performed by conventional methods: gram-negative rods were identified with the API 20E (Analytab Products, Plainville, N.Y.) and NF (Remel, Lenexa, Kans.) systems, the staphylococci were identified with StaphTrac (Analytab Products), and anaerobes were identified by methods described in the *Wadsworth Anaerobic Bacteriology Manual* (24). The susceptibility of the staphylococci to oxacillin was determined by the presence or absence of growth on an agar plate supplemented with 4% NaCl and containing 6 μg of oxacillin per ml and incubated at 35°C for 24 h (23). All isolates were stored frozen in skim milk at −70°C.

Antibiotics. Standard powders of CL 188,624 (3,5-*trans* diastereomers), CL 190,294 (3,5-*cis* diastereomers), and CL 191,121 (3,2, optically pure) were synthesized as described elsewhere (12). Biapenem was obtained from Wyeth-Ayerst Research, Pearl River, N.Y.; imipenem was obtained from Merck Sharp & Dohme, West Point, Pa.; meropenem was obtained from Zeneca, Chesire, United Kingdom; ceftazidime was obtained from Glaxo-Wellcome, Research Triangle Park, N.C.; oxacillin was obtained from Sigma Chemical Co., St. Louis, Mo.; and penicillin was obtained from the United States Pharmacopeia.

Susceptibility tests. The in vitro determination of the MICs was performed by the microtiter method as recommended by the National Committee for Clinical Laboratory Standards (16). Mueller-Hinton broth was used for assays with members of the family *Enterobacteriaceae*, staphylococci, and enterococci. The streptococci were tested in Mueller-Hinton broth supplemented with 5% sheep blood. Haemophilus test medium was used for assays with *Haemophilus influenzae* isolates. Microtiter plates in which each well contained 50 μl of twofold serial dilutions of the antimicrobial agents in the appropriate broth were inoculated with 50 μl of inoculum to yield a final density of 1×10^5 to 5×10^5 CFU/ml. Anaerobic bacteria were tested on Wilkins Chalgren agar supplemented with 5% lysed sheepblood and 0.001% vitamin K. The MICs were determined after 18 to 22 h of incubation at 35°C in ambient air for the aerobic bacteria and after 48 h in an anaerobic chamber (Coy Laboratories, Ann Arbor, Mich.) for the anaerobes. The MIC was defined as the lowest concentration of the antimicrobial agent that completely inhibits growth of the organism as detected by the unaided eye.

Time-kill curve studies. Bactericidal activity was determined by the time-kill curve method recommended by the National Committee for Clinical Laboratory Standards (17). Flasks containing 50 ml of the appropriate antimicrobial agent were inoculated with 50 ml of each test organism in the logarithmic growth phase (adjusted to a density of approximately 1×10^6 to 5×10^6 CFU/ml) to yield a drug concentration equivalent to four times the MIC. The flasks were incubated at 35°C in a shaking water bath. Aliquots were removed at 0, 2, 4, and 6 h and diluted, and 0.1 ml was plated in duplicate onto Trypticase soy agar plates. Total

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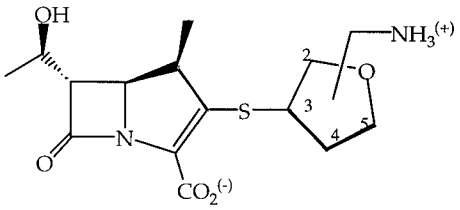

Compound	Stereochemistry
CL 191,121	3R, 2R
CL 188,624	3S, 5R & 3R, 5S (trans)
CL 190,294	3R, 5R & 3S, 5S (cis)

FIG. 1. Structures of the aminomethylTHF 1β-methylcarbapenems.

bacterial counts (CFU per milliliter) were determined after 18 h of incubation at 35°C. Bactericidal activity was defined as a 99.9% ($\geq$3 $\log_{10}$) reduction in the total count of the original inoculum.

PAE. The postantibiotic effects (PAEs) of CL 191,121 and imipenem against clinical isolates of *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae* were determined. Flasks containing 50 ml of the appropriate antimicrobial agent were inoculated with 50 ml of each test organism in the logarithmic growth phase (adjusted to a density of approximately 10^7 CFU/ml) to yield a drug concentration equivalent to four to eight times the MIC. The flasks were incubated with shaking for 2 h, followed by dilution of the culture to 1:1,000 in fresh, warm Mueller-Hinton broth. The flasks were returned to the shaker, aliquots were removed at selected time points and diluted, and 0.1 ml was plated in duplicate onto Trypticase soy agar plates. The PAE was defined as $T - C$, where T is the time required for the count in CFU in the test culture to increase 1 $\log_{10}$ above the count immediately after drug removal, and C is the corresponding time for the control culture (2).

RESULTS

The in vitro activities of CL 188,624, CL 190,294, CL 191,121, and the comparative carbapenems against a wide diversity of recent clinical gram-negative and gram-positive isolates are summarized in Tables 1 and 2, respectively.

The THF carbapenems demonstrated comparable activity against most of the gram-negative isolates tested. CL 191,121 (2-aminomethyl substitution) was slightly more active (twofold) than CL 188,624 and CL 190,294 (5-aminomethyl substitution) against *E. coli*, *Citrobacter diversus*, *Salmonella* spp., *Moraxella catarrhalis*, *Haemophilus influenzae*, *Acinetobacter calcoaceticus*, and *Bacteroides fragilis* and was two- to fourfold more active against methicillin-susceptible *Staphylococcus aureus* and coagulase-negative staphylococci, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus agalactiae*, and penicillin-resistant *Streptococcus pneumoniae*.

CL 191,121 was twofold more active than biapenem and two- to fourfold more active than imipenem against *E. coli*, *K. pneumoniae*, *Klebsiella oxytoca*, *C. diversus*, *Proteus mirabilis*, and *H. influenzae* isolates but was two- to fourfold less active than meropenem against *K. pneumoniae*, *K. oxytoca*, *P. mirabilis*, and *H. influenzae*. Against *Enterobacter cloacae*, *Enterobacter aerogenes*, *Citrobacter freundii*, *Morganella morganii*, and *Salmonella* isolates, CL 191,121 was twofold more active than imipenem, as active or twofold less active than biapenem, and four to eight times less active than meropenem. CL 191,121, biapenem, and imipenem demonstrated equivalent activities against clinical *Serratia*, *Shigella*, and *Providencia* isolates (MICs at which 90% of isolates are inhibited [MIC_{90}s], 2, 0.5, and 2 μg/ml, respectively). Meropenem was 2- to 16-fold more active than the other carbapenems against these isolates. Biapenem was two times more active than CL 191,121 and imipenem and four times more active than CL 188,624, CL 190,294, and meropenem against *Acinetobacter calcoaceticus* strains. None of the carbapenems demonstrated activity against the *Stenotrophomonas maltophilia* isolates tested. For ceftazidime-resistant *K. pneumoniae* isolates susceptibilities to all the carbapenems were comparable to those for the ceftazidime-susceptible isolates (twofold or lower increase in the MIC). Biapenem, imipenem, and meropenem were much more active (MIC_{50}s, 0.25, 1.0, and 0.5 μg/ml, respectively) than the THF carbapenems (MIC_{50}s, 4 to 8 μg/ml) against *Pseudomonas aeruginosa* isolates. The carbapenem MICs were elevated (MICs, $\geq$8 μg/ml) for 10% of the *Pseudomonas* strains. CL 191,121, biapenem, and imipenem demonstrated equivalent activities (MIC_{90}s, 0.5 μg/ml) and were twofold more active than CL 188,624, CL 190,294, and meropenem against 24 clinical isolates of *Bacteroides fragilis*. Imipenem was twofold more active than CL 191,121, fourfold more active than biapenem, and four- to eightfold more active than meropenem against methicillin-susceptible staphylococci (*S. aureus* as well as coagulase-negative staphylococci) (Table 2). None of the carbapenems exhibited activity against methicillin-resistant staphylococci (MIC_{90}s, >16 μg/ml). The susceptibilities of the *S. pneumoniae* strains varied with their susceptibilities to penicillin. The penicillin-resistant strains were less sensitive to the carbapenems than the penicillin-susceptible strains. The THF carbapenems, biapenem, and imipenem all had similar activities against penicillin-susceptible (MIC_{90}s, $\leq$0.015 μg/ml) and penicillin-intermediate (MIC_{90}s, 0.12 μg/ml) strains. CL 191,121, imipenem, and biapenem were twofold more active (MIC_{90}s, 1 μg/ml) than meropenem against penicillin-resistant strains of *S. pneumoniae*. All the carbapenems had excellent activities (MIC_{90}s, $\leq$0.06 μg/ml) against *Streptococcus pyogenes*. CL 191,121 and imipenem were twofold more active than biapenem and fourfold more active than meropenem against *S. agalactiae*. CL 191,121 and imipenem had moderate activities (MIC_{90}s, 1 μg/ml) against *E. faecalis* isolates. Biapenem and meropenem were two- and fourfold less active, respectively, than CL 191,121 and imipenem. All the carbapenems displayed poor activities (MIC_{90}s, 64 to >128 μg/ml) against the *E. faecium* isolates tested.

Each of the carbapenems demonstrated fairly rapid cidal activities against *E. coli* 311 and *S. aureus* Smith by time-kill curve studies (Fig. 2 and 3, respectively). At 6 h the THF carbapenems demonstrated bactericidal activity (>1 $\log_{10}$) greater than those of biapenem, imipenem, and meropenem against *E. coli* 311. The use of CL 191,121 and CL 188,624 resulted in slightly greater reductions in viable cell counts (<1 $\log_{10}$) than the use of CL 190,294, biapenem, meropenem, and imipenem against the *S. aureus* strain.

Both CL 191,121 and imipenem exerted similar PAEs (0.7 and 0.9 h, respectively) against *S. aureus* PT4308, while the PAE of CL 191,121 was approximately 40% longer than that of imipenem (1.3 and 0.9 h, respectively) against the other *S. aureus* clinical isolate tested (Table 3). The PAEs of CL 191,121 and imipenem against the gram-negative isolates *E. coli* 311 and *K. pneumoniae* PT4696 were comparable, with the duration of the effect being between 1.3 and 1.6 h.

DISCUSSION

The carbapenems represent highly potent antimicrobial agents. Imipenem, biapenem, and meropenem have been extensively investigated and demonstrate excellent in vitro activities (7, 15, 20). In addition, several investigational carbapenems with dithiocarbamate, bicyclic imidazole, carboxyphenyl,

TABLE 1. In vitro activities of THF carbapenems and comparative agents against gram-negative bacteria

Organism (no. of isolates)	Antibiotic	MIC (μg/ml)		
		Range	50%	90%
Escherichia coli (30)	CL 188,624	0.06–0.12	0.06	0.12
	CL 190,294	0.03–0.06	0.06	0.06
	CL 191,121	≤0.015–0.06	0.03	0.03
	Biapenem	0.03–0.06	0.06	0.06
	Imipenem	0.12–0.25	0.12	0.25
	Meropenem	≤0.015–0.03	0.03	0.03
Escherichia coli, ceftazidime resistant (15)	CL 188,624	0.03–0.25	0.06	0.25
	CL 190,294	0.03–0.5	0.12	0.25
	CL 191,121	0.03–0.5	0.03	0.25
	Biapenem	0.03–0.25	0.03	0.12
	Imipenem	0.12–1.0	0.12	0.25
	Meropenem	≤0.015–0.12	0.03	0.12
Klebsiella pneumoniae (15)	CL 188,624	0.06–0.5	0.06	0.25
	CL 190,294	0.06–0.5	0.12	0.12
	CL 191,121	0.03–1.0	0.12	0.25
	Biapenem	0.03–1.0	0.12	0.5
	Imipenem	0.06–1.0	0.25	0.25
	Meropenem	0.03–0.12	0.03	0.12
Klebsiella pneumoniae, ceftazidime resistant (15)	CL 188,624	0.06–0.5	0.12	0.25
	CL 190,294	0.12–0.5	0.25	0.25
	CL 191,121	0.03–0.25	0.12	0.25
	Biapenem	0.03–0.25	0.12	0.25
	Imipenem	0.12–0.5	0.25	0.5
	Meropenem	0.03–0.12	0.06	0.06
Klebsiella oxytoca (15)	CL 188,624	0.03–0.25	0.12	0.25
	CL 190,294	0.03–0.25	0.12	0.25
	CL 191,121	0.03–0.25	0.12	0.25
	Biapenem	0.03–0.5	0.12	0.25
	Imipenem	0.12–0.5	0.25	0.5
	Meropenem	0.03–0.12	0.06	0.06
Serratia marcescens (15)	CL 188,624	0.12–0.5	0.25	0.5
	CL 190,294	0.12–0.5	0.25	0.5
	CL 191,121	0.25–4.0	1.0	2.0
	Biapenem	0.25–4.0	1.0	2.0
	Imipenem	0.25–4.0	1.0	4.0
	Meropenem	0.03–1.0	0.12	0.12
Enterobacter cloacae (11)	CL 188,624	0.03–0.25	0.12	0.25
	CL 190,294	0.06–0.25	0.12	0.25
	CL 191,121	0.06–0.5	0.12	0.25
	Biapenem	0.06–0.25	0.12	0.25
	Imipenem	0.5–2.0	0.5	1.0
	Meropenem	0.06–0.12	0.06	0.12
Enterobacter aerogenes (13)	CL 188,624	0.06–0.5	0.25	0.5
	CL 190,294	0.06–0.5	0.25	0.5
	CL 191,121	0.06–1.0	0.5	1.0
	Biapenem	0.06–1.0	0.25	0.5
	Imipenem	0.5–4.0	1.0	2.0
	Meropenem	0.03–0.12	0.06	0.12
Citrobacter freundii (15)	CL 188,624	0.03–0.5	0.12	0.25
	CL 190,294	0.06–0.5	0.06	0.25
	CL 191,121	0.03–1.0	0.12	0.5
	Biapenem	0.03–0.25	0.12	0.25
	Imipenem	0.12–2.0	1.0	2.0
	Meropenem	0.03–0.25	0.03	0.12
Citrobacter diversus (15)	CL 188,624	0.03–0.12	0.03	0.12
	CL 190,294	0.03–0.12	0.03	0.06
	CL 191,121	≤0.015–0.06	≤0.015	0.03
	Biapenem	0.03–0.12	0.03	0.06
	Imipenem	0.06–0.12	0.12	0.12
	Meropenem	≤0.015–0.03	≤0.015	0.03
Salmonella species (15)	CL 188,624	0.03–0.25	0.06	0.12
	CL 190,294	0.03–0.25	0.06	0.12
	CL 191,121	≤0.015–0.06	0.03	0.06
	Biapenem	≤0.06–0.12	0.03	0.06
	Imipenem	0.06–0.5	0.12	0.25
	Meropenem	≤0.015–0.06	0.03	0.06
Shigella species (15)	CL 188,624	0.12–0.5	0.25	0.25
	CL 190,294	0.12–0.5	0.25	0.25
	CL 191,121	0.25–0.5	0.25	0.5
	Biapenem	0.12–0.5	0.25	0.25
	Imipenem	0.25–0.5	0.25	0.5
	Meropenem	≤0.015–0.25	0.03	0.03
Morganella morganii (15)	CL 188,624	0.5–2.0	1.0	2.0
	CL 190,294	0.5–1.0	1.0	1.0
	CL 191,121	0.25–2.0	1.0	2.0
	Biapenem	0.25–2.0	1.0	2.0
	Imipenem	2.0–4.0	4.0	4.0
	Meropenem	0.06–0.5	0.25	0.5
Proteus mirabilis (15)	CL 188,624	0.25–2.0	1.0	2.0
	CL 190,294	0.25–2.0	1.0	2.0
	CL 191,121	0.06–2.0	1.0	2.0
	Biapenem	0.06–4.0	2.0	4.0
	Imipenem	0.12–4.0	2.0	4.0
	Meropenem	0.03–0.12	0.06	0.12
Providencia species (15)	CL 188,624	0.25–8.0	0.5	4.0
	CL 190,294	0.12–4.0	0.5	2.0
	CL 191,121	0.25–2.0	1.0	2.0
	Biapenem	0.25–2.0	1.0	2.0
	Imipenem	0.5–4.0	1.0	2.0
	Meropenem	0.06–1.0	0.06	0.12
Moraxella catarrhalis (15)	CL 188,624	≤0.015–0.06	0.03	0.03
	CL 190,294	≤0.015–0.06	0.03	0.06
	CL 191,121	≤0.015	≤0.015	≤0.015
	Biapenem	≤0.015–0.06	≤0.015	0.06
	Imipenem	≤0.015–0.06	≤0.015	0.06
	Meropenem	≤0.015	≤0.015	≤0.015
Burkholderia cepacia (12)	CL 188,624	2.0–8.0	8.0	8.0
	CL 190,294	4.0–16.0	8.0	16.0
	CL 191,121	4.0–16.0	8.0	16.0
	Biapenem	0.25–8.0	2.0	8.0
	Imipenem	1.0–16.0	8.0	16.0
	Meropenem	0.25–8.0	2.0	8.0
Stenotrophomonas maltophilia (20)	CL 188,624	256.0–>256.0	>256.0	>256.0
	CL 190,294	256.0–>256.0	>256.0	>256.0
	CL 191,121	256.0–>256.0	>256.0	>256.0
	Biapenem	256.0–>256.0	>256.0	>256.0
	Imipenem	256.0–>256.0	256.0	>256.0
	Meropenem	64.0–>256.0	256.0	256.0
Haemophilus influenzae (30)	CL 188,624	0.12–2.0	0.5	1.0
	CL 190,294	0.12–2.0	0.5	1.0
	CL 191,121	≤0.015–4.0	0.25	0.5
	Biapenem	≤0.015–4.0	0.5	1.0
	Imipenem	0.06–4.0	0.5	1.0
	Meropenem	≤0.015–0.12	0.06	0.06
Bacteroides fragilis (24)	CL 188,624	0.5–32.0	0.5	1.0
	CL 190,294	0.25–16.0	0.5	1.0
	CL 191,121	0.06–8.0	0.12	0.5
	Biapenem	0.06–0.5	0.25	0.25
	Imipenem	0.06–2.0	0.25	0.5
	Meropenem	0.06–4.0	0.25	1.0
Acinetobacter calcoaceticus (15)	CL 188,624	0.12–1.0	0.25	1.0
	CL 190,294	0.12–2.0	0.25	1.0
	CL 191,121	0.06–1.0	0.25	0.5
	Biapenem	0.03–0.25	0.12	0.25
	Imipenem	0.12–0.5	0.25	0.5
	Meropenem	0.12–1.0	0.5	1.0
Pseudomonas aeruginosa (30)	CL 188,624	2.0–>16.0	8.0	16.0
	CL 190,294	2.0–>16.0	8.0	16.0
	CL 191,121	1.0–16.0	4.0	8.0
	Biapenem	0.12–16.0	0.25	4.0
	Imipenem	0.5–16.0	1.0	4.0
	Meropenem	0.06–>16.0	0.5	8.0

TABLE 2. In vitro activities of THF carbapenems and comparative agents against gram-positive bacteria

Organism (no. of isolates)	Antibiotic	MIC (μg/ml)		
		Range	50%	90%
Streptococcus pneumoniae, penicillin susceptible (15)	CL 188,624	≤0.015–0.06	≤0.015	≤0.015
	CL 190,294	≤0.015–0.06	≤0.015	≤0.015
	CL 191,121	≤0.015	≤0.015	≤0.015
	Biapenem	≤0.015–0.06	≤0.015	≤0.015
	Imipenem	≤0.015–0.03	≤0.015	≤0.015
	Meropenem	≤0.015–0.06	≤0.015	≤0.015
Streptococcus pneumoniae, penicillin intermediate (12)	CL 188,624	0.03–0.25	0.12	0.12
	CL 190,294	0.03–0.25	0.12	0.12
	CL 191,121	0.03–0.25	0.12	0.12
	Biapenem	0.03–0.25	0.06	0.12
	Imipenem	≤0.015–0.12	0.03	0.12
	Meropenem	0.06–0.25	0.12	0.25
Streptococcus pneumoniae, penicillin resistant (15)	CL 188,624	0.06–2.0	1.0	2.0
	CL 190,294	0.12–2.0	1.0	2.0
	CL 191,121	0.12–1.0	0.5	1.0
	Biapenem	0.12–1.0	0.5	1.0
	Imipenem	0.12–1.0	0.25	1.0
	Meropenem	0.5–2.0	0.5	2.0
Streptococcus pyogenes (15)	CL 188,624	≤0.06–0.12	≤0.06	≤0.06
	CL 190,294	≤0.06–0.12	≤0.06	≤0.06
	CL 191,121	≤0.015	≤0.015	≤0.015
	Biapenem	≤0.015	≤0.015	≤0.015
	Imipenem	≤0.015	≤0.015	≤0.015
	Meropenem	≤0.015	≤0.015	≤0.015
Staphylococcus aureus, methicillin susceptible (15)	CL 188,624	0.25–0.5	0.25	0.25
	CL 190,294	0.06–0.25	0.12	0.12
	CL 191,121	0.03–0.06	0.06	0.06
	Biapenem	0.03–0.12	0.06	0.12
	Imipenem	≤0.015–0.03	≤0.015	0.03
	Meropenem	0.12–0.25	0.12	0.25
Coagulase-negative staphylococcus, methicillin susceptible (15)	CL 188,624	0.12–1.0	0.25	0.5
	CL 190,294	0.03–0.5	0.12	0.25
	CL 191,121	≤0.015–0.12	0.03	0.12
	Biapenem	0.03–0.25	0.06	0.12
	Imipenem	≤0.015–0.06	≤0.015	0.06
	Meropenem	0.06–0.5	0.12	0.5
Staphylococcus aureus, methicillin resistant (29)	CL 188,624	1.0–>16.0	16.0	>16.0
	CL 190,294	0.5–>16.0	8.0	>16.0
	CL 191,121	0.06–>16.0	>16.0	>16.0
	Biapenem	0.12–>16.0	>16.0	>16.0
	Imipenem	≤0.015–>16.0	>16.0	>16.0
	Meropenem	0.25–>16.0	>16.0	>16.0
Coagulase-negative staphylococcus, methicillin resistant (15)	CL 188,624	2.0–>16.0	>16.0	>16.0
	CL 190,294	2.0–>16.0	>16.0	>16.0
	CL 191,121	0.5–>16.0	16.0	>16.0
	Biapenem	2.0–>16.0	>16.0	>16.0
	Imipenem	0.25–>16.0	>16.0	>16.0
	Meropenem	4.0–>16.0	>16.0	>16.0
Streptococcus agalactiae (15)	CL 188,624	≤0.015–0.06	0.03	0.03
	CL 190,294	0.03–0.06	0.06	0.06
	CL 191,121	≤0.015–0.03	≤0.015	≤0.015
	Biapenem	≤0.015–0.03	≤0.015	0.03
	Imipenem	≤0.015	≤0.015	≤0.015
	Meropenem	0.03–0.12	0.06	0.06
Enterococcus faecalis (15)	CL 188,624	1.0–8.0	2.0	8.0
	CL 190,294	1.0–8.0	1.0	8.0
	CL 191,121	0.25–2.0	0.5	1.0
	Biapenem	0.5–8.0	2.0	2.0
	Imipenem	0.25–2.0	1.0	1.0
	Meropenem	1.0–16.0	4.0	4.0
Enterococcus faecium (13)	CL 188,624	0.5–>128.0	8.0	128.0
	CL 190,294	0.5–>128.0	8.0	128.0
	CL 191,121	0.25–128.0	8.0	64.0
	Biapenem	0.5–>128.0	32.0	>128.0
	Imipenem	0.25–>128.0	8.0	64.0
	Meropenem	1.0–>128.0	32.0	128.0

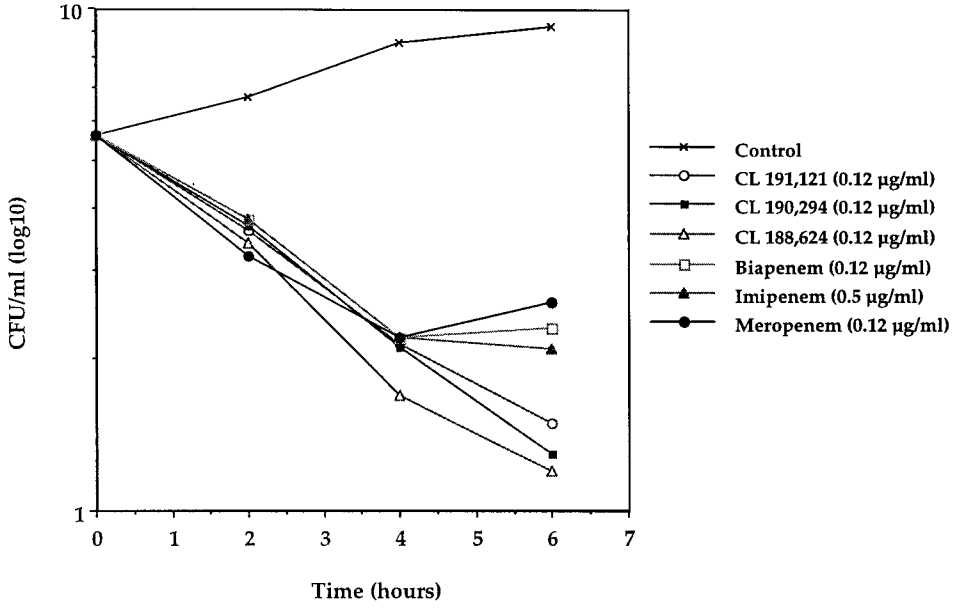

FIG. 2. Antibacterial activities of carbapenems against *E. coli* 311.

and pyrrolidine side chains have been reported to have potent activities against gram-negative and gram-positive organisms (5, 8, 15, 19, 25, 26). CL 188,624, CL 190,294, and CL 191,121 are 1β-methylcarbapenems with a novel aminomethyl-substituted tetrahydrofuranylthio moiety at the 2 position of the carbapenem molecule. They have good affinities of binding to penicillin-binding proteins in gram-positive and gram-negative bacteria, as noted by Bush et al. (1), and demonstrate excellent in vitro activities against a wide range of gram-negative and gram-positive isolates with the exception of *Pseudomonas* and *Stenotrophomonas* isolates, methicillin-resistant staphylococci, and *E. faecium*. The THF carbapenems, like other carbapenems, are stable to hydrolysis by the majority of common β-lactamases (10, 27). It was noted that the THF carbapenems had comparable activities against ceftazidime-susceptible and ceftazidime-resistant, extended-spectrum β-lactamase-producing *E. coli* and *K. pneumoniae* isolates. In general, among the THF carbapenems, the 3,2-substituted THF carbapenem CL 191,121 was slightly more active than the 3,5-substituted compounds CL 188,624 and CL 190,294 against gram-positive isolates and *Moraxella* isolates. There were no significant differences in activity between the *cis*- and *trans*-3,5-substituted isomers. In comparison with other carbapenem antibiotics, the THF carbapenems were more active than imipenem, as active as biapenem, and less active than meropenem against gram-negative isolates. One of these compounds, CL 191,121, was more active than biapenem and meropenem and was as active as imipenem against gram-positive isolates and was slightly more active than imipenem against most gram-negative isolates.

The excellent in vitro activities of the THF carbapenems, in

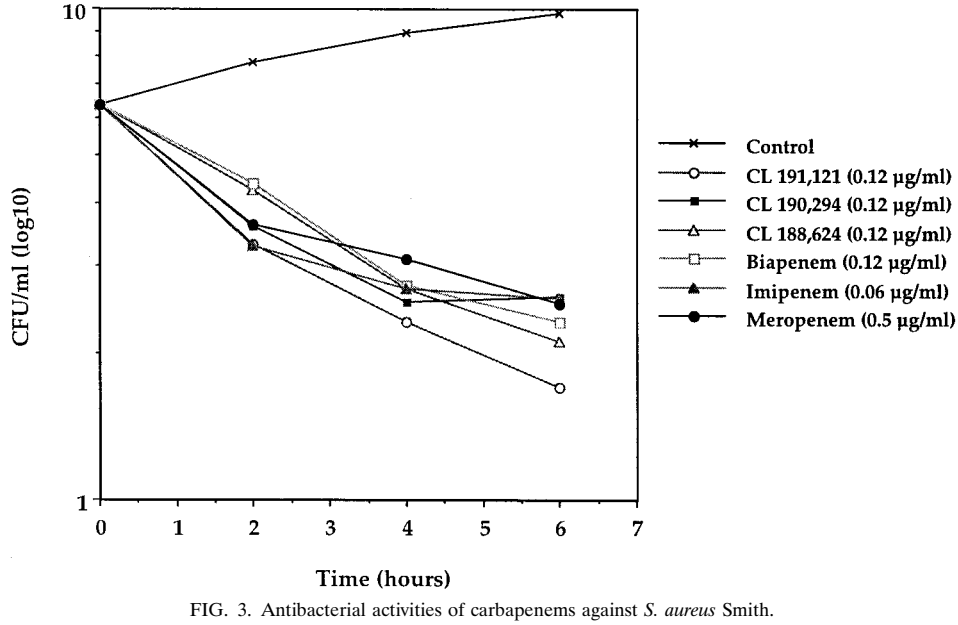

FIG. 3. Antibacterial activities of carbapenems against *S. aureus* Smith.

TABLE 3. PAEs of CL 191,121 and imipenem

Organism	Strain	PAE (h)	
		CL 191,121	Imipenem
Staphylococcus aureus	PT4308	0.7	0.9
Staphylococcus aureus	PT5635	1.3	0.9
Escherichia coli	311	1.6	1.4
Klebsiella pneumoniae	PT4696	1.3	1.3

particular, CL 191,121, against a wide range of gram-negative and gram-positive isolates, combined with their rapid cidal activities, moderate PAEs, and stability to β-lactamases and dehydropeptidases, make them excellent candidates for further investigations.

ACKNOWLEDGMENTS

We thank Lynetta Lieberman, Mary Whatley, and Teri Popkave for superb technical assistance.

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