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Comparative In Vitro Activities of L-695,256, a Novel Carbapenem, against Gram-Positive Bacteria

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The in vitro activity of a prototype 2-aryl carbapenem, L-695,256, against gram-positive bacteria was examined. All streptococci and oxacillin-susceptible and -resistant staphylococci were inhibited at concentrations of ≤0.125, ≤0.125, and 4 μg/ml, respectively. The activity of L-695,256 was superior to that of imipenem against other organisms intrinsically resistant to β-lactams.

The introduction of imipenem into clinical practice represented a major advance. Its broad antibacterial spectrum is potentially advantageous for empiric treatment of infections prior to identification of causative organisms and for treatment of polymicrobial infections. In addition, because of resistance to hydrolysis by most clinically important β-lactamases and other favorable characteristics, this carbapenem often retains activity against nosocomial isolates of gram-negative bacteria resistant to other β-lactam antibiotics (3, 4, 18). Two notable exceptions to this favorable pattern of activity are methicillin-resistant staphylococci and penicillin-resistant enterococci, both of which display reduced susceptibility to imipenem (20). In both instances, resistance to β-lactams can be attributed to the presence of penicillin-binding proteins with reduced affinities for these agents (7, 8, 14, 16, 22). Neither of the two more recently developed carbapenems, meropenem and biapenem, offers any activity advantage over imipenem against these organisms in particular or against gram-positive bacteria in general (13, 20).

L-695,256 (Fig. 1) is one of a series of novel 2-aryl carbapenems selected for evaluation because of its unusually good activity against methicillin-resistant staphylococci (19). This drug binds to PBP 2a of *Staphylococcus aureus* and to PBP 5 of *Enterococcus hirae* with substantially greater affinity than comparable β-lactams (6, 9). The present study was undertaken to examine the in vitro activity of L-695,256 against a variety of gram-positive bacteria, including strains specifically collected because of their resistance to β-lactams or other antibiotics.

(This work was presented in part at the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, Fla., October 1994 [12].)

Most of the organisms included in this study were clinical isolates obtained at Deaconess Hospital and Massachusetts General Hospital, Boston, Mass. Strains of streptococci demonstrating resistance to β-lactams and strains of vancomycin-resistant enterococci had been referred to our collection from a variety of sources (13, 20). L-695,256 and imipenem were provided by Merck, Sharp & Dohme Research Laboratories, Rahway, N.J. Other susceptibility reference powders were gifts from the indicated sources: oxacillin, Bristol-Myers Squibb Co., Syracuse, N.Y.; clindamycin, Upjohn Co., Kalamazoo, Mich.; erythromycin and vancomycin, Eli Lilly & Co., Indianapolis, Ind.; and teicoplanin, Marion Merrell Dow, Inc., Cincinnati, Ohio.

Antimicrobial susceptibility was determined by an agar dilution technique as previously described (13). Mueller-Hinton II agar (Becton Dickinson Microbiology Systems, Cockeysville, Md.) was used and was supplemented with 5% sheep blood when streptococci, diphtheroids, lactobacilli, pediococci, and *Leuconostoc* spp. were tested. Bacterial suspensions in Mueller-Hinton broth were applied with a replicating device yielding inocula of approximately 10^4 CFU. Plates were read after 18 to 20 h of incubation except for plates containing diphtheroids, which were incubated for 48 h to allow adequate growth.

To examine the bactericidal activity of the new carbapenem against enterococci, three highly gentamicin-resistant strains of *Enterococcus faecalis* were studied by time-kill methods. Bacteria were suspended to a concentration of 10^6 CFU/ml in glucose phosphate broth containing L-695,256 at eight times the MIC (2 μg/ml) or at 20 μg/ml. Flasks were incubated 24 h at 35°C without agitation, and samples were removed at 0, 4, and 24 h for colony counts, which were determined in duplicate. No attempt to inactivate the antibiotic prior to colony count determination was made.

The in vitro activities of L-695,256 and comparable agents are shown in Table 1. All isolates of oxacillin-susceptible staphylococci were inhibited by both imipenem and the new agent at low concentrations. In contrast, on the basis of either the MIC at which 50% of the isolates are inhibited or the MIC at which 90% of the isolates are inhibited, L-695,256 was 32- to 64-fold more active than imipenem against oxacillin-resistant staphylococci, inhibiting all strains at concentrations of ≤4 μg/ml. All streptococci were susceptible to L-695,256 at ≤0.125 μg/ml. L-695,256 was eightfold more active than imipenem against

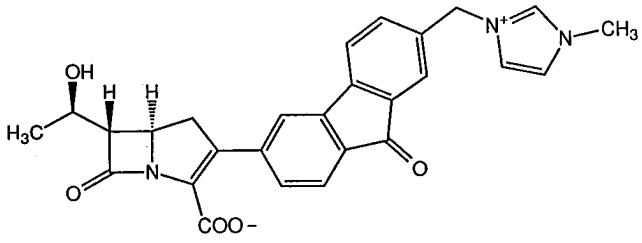

FIG. 1. Chemical structure of (5*R*, 6*S*)-2-[7-(1-methylimidazolium-3-yl) methyl-9-fluorenone-3-yl]-6-(1*R*-hydroxyethyl)-carbapen-2-em-3-carboxylate (L-695,256).

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TABLE 1. In vitro activities of L-695,256 and other antimicrobial agents against gram-positive bacteria

Organism (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]		
		Range	50%	90%
S. aureus (methicillin susceptible) (40)	L-695,256	≤0.06–0.125	≤0.06	≤0.06
	Imipenem	0.03–0.06	0.03	0.06
	Oxacillin	0.25–0.5	0.5	0.5
	Penicillin	0.06–64	8	64
	Vancomycin	1–2	1	1
	Teicoplanin	0.5–4	1	1
	Erythromycin	0.25–>128	0.5	4
	Clindamycin	0.125–128	0.125	0.125
S. aureus (methicillin resistant) (27)	L695-,256	0.5–4	2	2
	Imipenem	4–256	128	128
	Oxacillin	≥128	>128	>128
	Penicillin	16–64	64	64
	Vancomycin	1–2	2	2
	Teicoplanin	0.5–2	1	2
	Erythromycin	8–>128	>128	>128
	Clindamycin	0.125–>128	>128	>128
Staphylococcus epidermidis (methicillin susceptible) (13)	L-695,256	≤0.06–0.125	≤0.06	0.125
	Imipenem	≤0.06–0.5	0.125	0.5
	Oxacillin	0.125–1	0.25	0.5
	Penicillin	≤0.06–64	8	64
	Vancomycin	1–2	2	2
	Teicoplanin	0.25–4	2	2
	Erythromycin	0.125–>128	0.5	>128
	Clindamycin	≤0.06–>128	0.25	>128
S. epidermidis (methicillin resistant) (40)	L-695,256	≤0.06–2	0.5	1
	Imipenem	≤0.06–32	16	32
	Oxacillin	4–>128	64	>128
	Penicillin	2–64	32	64
	Vancomycin	2–4	2	4
	Teicoplanin	2–8	4	8
	Erythromycin	0.25–>128	>128	>128
	Clindamycin	0.06–>128	>128	>128
S. aureus (borderline oxacillin resistant) (6)	L-695,256	0.125–0.25		
	Imipenem	0.125–0.5		
	Oxacillin	2–4		
	Penicillin	16–64		
	Vancomycin	1		
	Teicoplanin	0.5–2		
	Erythromycin	0.25–>128		
	Clindamycin	0.125–0.5		
E. faecalis (20)	L-695,256	0.125–0.25	0.25	0.25
	Imipenem	0.125–2	2	2
	Oxacillin	8–16	16	16
	Penicillin	2–4	2	4
	Vancomycin	2–4	2	2
	Teicoplanin	0.5–1	0.5	0.5
	Erythromycin	0.25–>128	2	4
	Clindamycin	16–>128	32	32
E. faecalis (HLGR, BLA+) (20)	L-695,256	0.125–0.5	0.125	0.5
	Imipenem	1–4	2	4
	Oxacillin	16–>128	16	>128
	Penicillin	4–8	4	8
	Vancomycin	1–4	2	2
	Teicoplanin	0.25–1	0.5	0.5
	Erythromycin	4–>128	>128	>128
	Clindamycin	8–>128	>128	>128
E. faecalis (vancomycin resistant) (10)	L-695,256	0.125–0.5	0.25	0.5
	Imipenem	1–16	4	4
	Oxacillin	8–128	128	128
	Penicillin	2–8	4	4
	Vancomycin	>256	>256	>256

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TABLE 1—*Continued*

Organism (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]		
		Range	50%	90%
	Teicoplanin	0.5–1	0.5	0.5
	Erythromycin	4–>128	>128	>128
	Clindamycin	12.8–>128	>128	>128
E. faecium (20)	L-695,256	0.25–32	4	16
	Imipenem	2–256	32	128
	Oxacillin	32–>128	>128	>128
	Penicillin	1–>128	32	128
	Vancomycin	1–8	1	2
	Teicoplanin	0.25–1	0.5	1
	Erythromycin	0.25–>128	>128	>128
	Clindamycin	0.125–>128	128	>128
E. faecium (HLGR) (10)	L-695,256	8–32	16	32
	Imipenem	≥256	256	>256
	Oxacillin	>128	>128	>128
	Penicillin	≥256	256	>256
	Vancomycin	0.5–1	1	1
	Teicoplanin	0.25–1	0.5	1
	Erythromycin	>128	>128	>128
	Clindamycin	>128	>128	>128
E. faecium (vancomycin resistant) (10)	L-695,256	≤0.06–32	16	32
	Imipenem	1–256	256	>256
	Oxacillin	32–128	>128	>128
	Penicillin	2–>256	256	>256
	Vancomycin	64–>256	>256	>256
	Teicoplanin	0.25–>256	0.5	>256
	Erythromycin	2–>128	>128	>128
	Clindamycin	0.2–>128	>128	>128
Enterococcus casseliflavus/*Enterococcus gallinarum* (6)	L-695,256	0.125–0.25		
	Imipenem	1–4		
	Oxacillin	64–>128		
	Penicillin	1–4		
	Vancomycin	8		
	Teicoplanin	0.5–1		
	Erythromycin	0.25–>128		
	Clindamycin	≥128		
Enterococcus avium (10)	L-695,256	0.125–0.5	0.5	0.5
	Imipenem	0.5–2	1	2
	Oxacillin	8–64	16	32
	Penicillin	1–2	1	1
	Vancomycin	1	1	1
	Teicoplanin	0.125–0.5	0.25	0.25
	Erythromycin	0.25–>128	16	>128
	Clindamycin	6.4–>128	12.8	>128
Enterococcus raffinosus (10)	L-695,256	8–16	16	16
	Imipenem	32–128	128	128
	Oxacillin	>128	>128	>128
	Penicillin	16–128	32	128
	Vancomycin	1–2	1	1
	Teicoplanin	0.25	0.25	0.25
	Erythromycin	≥128	>128	>128
	Clindamycin	6.4–>128	>128	>128
L. monocytogenes (20)	L-695,256	≤0.06–0.5	0.5	0.5
	Imipenem	0.125–1	0.25	0.5
	Oxacillin	0.5–4	4	4
	Penicillin	0.125–2	1	1
	Vancomycin	1–4	1	2
	Teicoplanin	0.25–1	0.5	0.5
	Erythromycin	0.25–2	0.5	1
	Clindamycin	2–16	8	16

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TABLE 1—*Continued*

Organism (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]		
		Range	50%	90%
Diphtheroids (*C. jeikeium*) (10)	L-695,256	0.06–128	0.25	32
	Imipenem	0.125–≥128	0.5	≥128
	Oxacillin	32–≥128	≥128	≥128
	Penicillin	4–≥128	4	≥128
	Vancomycin	0.5–2	1	1
	Teicoplanin	0.5	0.5	0.5
	Erythromycin	0.06–≥64	0.25	8
	Clindamycin	0.5–≥64	8	≥64
Streptococcus pneumoniae (penicillin susceptible) (11)	L-695,256	≤0.015	≤0.015	≤0.015
	Imipenem	≤0.015	≤0.015	≤0.015
	Oxacillin	0.06–0.5	0.125	0.125
	Penicillin	≤0.015–0.03	0.03	0.03
	Vancomycin	0.25–0.5	0.25	0.5
	Teicoplanin	0.06–0.125	0.125	0.125
	Erythromycin	0.06–0.125	0.06	0.125
	Clindamycin	0.03–0.25	0.125	0.125
S. pneumoniae (penicillin resistant) (9)	L-695,256	≤0.015–0.06		
	Imipenem	0.06–0.5		
	Oxacillin	2–32		
	Penicillin	0.25–8		
	Vancomycin	0.25–0.5		
	Teicoplanin	0.125		
	Erythromycin	0.06–>32		
	Clindamycin	0.125–32		
Viridans group streptococci (penicillin susceptible) (20)	L-695,256	≤0.015–0.06	0.03	0.06
	Imipenem	0.03–0.25	0.06	0.25
	Oxacillin	0.125–2	0.5	1
	Penicillin	≤0.015–0.125	0.06	0.125
	Vancomycin	0.5–1	1	1
	Teicoplanin	0.06–0.25	0.125	0.25
	Erythromycin	0.06–0.25	0.125	0.125
	Clindamycin	0.06–0.25	0.125	0.25
Viridans group streptococci (penicillin resistant) (10)	L-695,256	0.06–0.125	0.06	0.125
	Imipenem	0.25–1	0.5	1
	Oxacillin	4–32	16	16
	Penicillin	1–16	2	4
	Vancomycin	0.5–1	0.5	1
	Teicoplanin	0.125–0.25	0.125	0.25
	Erythromycin	0.125–≥64	8	≥64
	Clindamycin	0.06–≥4	0.06	0.25
Streptococci, groups A, C, and G (20)	L-695,256	≤0.015	≤0.015	≤0.015
	Imipenem	0.015–0.06	0.015	0.03
	Oxacillin	0.06–0.125	0.125	0.125
	Penicillin	≤0.015–0.06	≤0.015	≤0.015
	Vancomycin	0.5–1	0.5	0.5
	Teicoplanin	0.25–0.5	0.25	0.5
	Erythromycin	0.03–0.06	0.06	0.06
	Clindamycin	0.125	0.125	0.125
Streptococci, group B (10)	L-695,256	0.03–0.06	0.03	0.06
	Imipenem	0.06–0.125	0.06	0.06
	Oxacillin	0.25–4	1	1
	Penicillin	0.06–0.25	0.06	0.125
	Vancomycin	1	1	1
	Teicoplanin	0.5–1	0.5	1
	Erythromycin	0.06	0.06	0.06
	Clindamycin	0.125–0.25	0.125	0.125
Lactobacillus spp. (12)	L-695,256	≤0.06–1	0.25	0.5
	Imipenem	≤0.06–8	2	4
	Oxacillin	2–32	8	32

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TABLE 1—*Continued*

Organism (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]		
		Range	50%	90%
	Penicillin	0.125–4	0.5	4
	Vancomycin	>256	>256	>256
	Teicoplanin	≥128	>128	>128
	Erythromycin	≤0.06–0.25	0.125	0.25
	Clindamycin	≤0.06–0.5	0.125	0.25
Leuconostoc spp. (10)	L-695,256	≤0.06–1	0.5	1
	Imipenem	0.125–16	4	8
	Oxacillin	2–16	8	8
	Penicillin	0.125–1	0.25	0.25
	Vancomycin	>256	>256	>256
	Teicoplanin	≥128	128	>128
	Erythromycin	0.125–0.25	0.125	0.25
	Clindamycin	≤0.06–0.25	0.06	0.25
Pediococcus spp. (6)	L-695,256	≤0.06–0.5		
	Imipenem	0.25–1		
	Oxacillin	8		
	Penicillin	0.5–1		
	Vancomycin	>256		
	Teicoplanin	>256		
	Erythromycin	0.125–0.25		
	Clindamycin	≤0.06		
Erysipelothrix spp. (2)	L-695,256	≤0.06		
	Imipenem	≤0.06		
	Oxacillin	≤0.06		
	Penicillin	≤0.06		
	Vancomycin	32		
	Teicoplanin	1		
	Erythromycin	0.25–0.5		
	Clindamycin	≤0.06		

[a] HLGR, high-level gentamicin resistance; BLA+, β-lactamase producer.
[b] 50% and 90%, MICs at which 50 and 90% of the isolates are inhibited.
[c] One and five strains, respectively.

penicillin-resistant strains of pneumococci and viridans streptococci, among which were 11 isolates for which MICs of penicillin exceeded 1.0 μg/ml. L-695,256 was 4- to 16-fold more active than imipenem or penicillin against enterococci. Ninety percent of the vancomycin-resistant *E. faecalis* isolates were inhibited by 0.5 μg of the new compound per ml compared with 4 μg of penicillin or imipenem per ml. Strains of *Enterococcus faecium* and *Enterococcus raffinosus* (and *Corynebacterium jeikeium*) were more resistant to all β-lactams tested, but against these, L-695,256 was again more active than penicillin or imipenem. L-695,256 was eightfold more active than imipenem against *Leuconostoc* spp. and *Lactobacillus* spp., but the two drugs had comparable activities against *Listeria monocytogenes*, *Pediococcus* spp. and two strains of *Erysipelothrix*.

The new carbapenem demonstrated bacteriostatic activity against three isolates of *E. faecalis* by the time-kill method. At either 2 or 20 μg/ml, a reduction of ≤1 $\log_{10}$ CFU/ml in viable organisms relative to the inoculum was observed at 4 h of incubation, and a rate of killing of ≤2 $\log_{10}$ CFU/ml was noted by 24 h of incubation.

The new 2-aryl carbapenem, L-695,256, proved to be at least as active as imipenem against a broad range of gram-positive bacteria studied here. In particular, L-695,256 was substantially more active than imipenem against oxacillin-resistant staphylococci and highly penicillin-resistant enterococci. Concentrations of the new drug inhibiting 90% of isolates in this study were virtually identical to concentrations observed and reported in preliminary form by others, including those determined by agar dilution (17) and by broth microdilution with 2% NaCl supplementation (10).

The unusual activity of L-695,256 in vitro against gram-positive organisms that are intrinsically resistant to β-lactam antibiotics because of the presence of low-affinity penicillin-binding protein targets appears to be related to the enhanced binding affinity of this agent compared with that of imipenem for PBP 2a of staphylococci (6, 9) and PBP 5 of enterococci (9). The potential relevance of these observations to in vivo infection is supported by studies showing the 2-aryl carbapenem to be more active than imipenem in animal models of infection caused by a homogeneously methicillin-resistant strain of *S. aureus* (6, 21).

Methicillin resistance in *S. aureus* has been recognized as a significant clinical problem for more than two decades (2). The importance of methicillin-resistant coagulase-negative staphylococci as nosocomial pathogens has been increasingly appreciated (1, 11). In light of the increasing prevalence of vancomycin-resistant (and multiply drug-resistant) enterococci among hospital isolates since 1989 (5) and the demonstration of the transferability of vancomycin resistance from enterococci to *S. aureus* under experimental conditions (15), there is serious concern that vancomycin resistance may emerge among clinical isolates of methicillin-resistant staphylococci, with devastating consequences.

On the basis of its in vitro activity against staphylococci,

enterococci, and streptococci that have reduced susceptibility to β-lactams at the target level, L-695,256 appears to be an important prototype for the development of novel carbapenems with enhanced activity against these organisms.

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REFERENCES

1. **Boyce, J. M., G. Potter-Bynoe, S. M. Opal, L. Dziobek, and A. A. Medeiros.** 1990. A common-source outbreak of *Staphylococcus epidermidis* infections among patients undergoing cardiac surgery. J. Infect. Dis. **161:**493–499.
2. **Brumfitt, W., and J. Hamilton-Miller.** 1989. Methicillin-resistant *Staphylococcus aureus*. N. Engl. J. Med. **320:**1188–1196.
3. **Bush, K.** 1989. Classification of β-lactamases: groups 1, 2a, 2b, and 2b′. Antimicrob. Agents Chemother. **33:**264–270.
4. **Bush, K.** 1989. Classification of β-lactamases: groups 2c, 2d, 2e, 3, and 4. Antimicrob. Agents Chemother. **33:**271–276.
5. **Centers for Disease Control and Prevention.** 1994. Addressing emerging infectious disease threats: a prevention strategy for the United States (executive summary). Morbid. Mortal. Weekly Rep. **43:**1–18.
6. **Chambers, H. F.** 1994. In vitro and in vivo activity of L-695,256 [L] against methicillin-resistant *Staphylococcus aureus*. [MRSA], abstr. B85, p. 151. *In* Abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
7. **Chambers, H. F., M. Sachdeva, and S. Kennedy.** 1990. Binding affinity for penicillin-binding protein 2a correlates with in vivo activity of β-lactam antibiotics against methicillin-resistant *Staphylococcus aureus*. J. Infect. Dis. **162:**705–710.
8. **Grayson, M. L., G. M. Eliopoulos, C. B. Wennersten, K. L. Ruoff, P. C. De Girolami, M.-J. Ferraro, and R. C. Moellering, Jr.** 1991. Increasing resistance to β-lactam antibiotics among clinical isolates of *Enterococcus faecium*: a 22-year review at one institution. Antimicrob. Agents Chemother. **35:**2180–2184.
9. **Hammond, G. G., K. M. Overbye, and L. L. Silver.** 1994. Binding of L-695,256, a prototypical 2-aryl carbapenem antibiotic, to penicillin binding proteins of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus hirae*, abstr. F62, p. 127. *In* Abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
10. **Huber, J., B. Pelak, K. Dorso, L. Gerckens, E. St Rose, J. Kohler, S. Dufresne, J. Kahan, D. Shungu, and H. Kropp.** 1994. Antimicrobial profile of L-695,256: the prototype MRS-active 2-aryl carbapenem antibiotic, abstr. F54, p. 126. *In* Abstracts of the 34th Intersciences Conference Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
11. **Kernodle, D. S., N. L. Barg, and A. B. Kaiser.** 1988. Low-level colonization of hospitalized patients with methicillin-resistant coagulase-negative staphylococci and emergence of the organisms during surgical antimicrobial prophylaxis. Antimicrob. Agents Chemother. **32:**202–208.
12. **Malanoski, G., L. Collins, C. T. Eliopoulos, R. C. Moellering, Jr., and G. M. Eliopoulos.** 1994. Comparative in vitro activity of L-695,256, a novel carbapenem, abstr. F52, p. 126. *In* Abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
13. **Malanoski, G. J., L. Collins, C. Wennersten, R. C. Moellering, Jr., and G. M. Eliopoulos.** 1993. In vitro activity of biapenem against clinical isolates of gram-positive and gram-negative bacteria. Antimicrob. Agents Chemother. **37:**2009–2016.
14. **Murakami, K., and A. Tomasz.** 1989. Involvement of multiple genetic determinants in high-level methicillin resistance in *Staphylococcus aureus*. J. Bacteriol. **171:**874–879.
15. **Noble, W. C., Z. Virani, and R. G. A. Cree.** 1992. Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus*. FEMS Microbiol. Lett. **93:**195–198.
16. **Pierre, J., R. Williamson, M. Bornet, and L. Gutmann.** 1990. Presence of an additional penicillin-binding protein in methicillin-resistant *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, and *Staphylococcus simulans* with a low affinity for methicillin, cephalothin, and cefamandole. Antimicrob. Agents Chemother. **34:**1691–1694.
17. **Rylander, M., J. Rollof, and S. R. Norrby.** 1994. In vitro activity of L-695,256, a carbapenem active against multiply resistant Gram-positives, abstr. F56, p. 126. *In* Abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
18. **Sanders, C. C., and W. E. Sanders, Jr.** 1986. Type I β-lactamases of Gram-negative bacteria: interactions with β-lactam antibiotics. J. Infect. Dis. **154:** 792–800.
19. **Sasor, M., L. Cama, M. L. Greenlee, F. P. Dininno, and J. V. Heck.** 1994. The synthesis and structure-activity relationships of a series of 2-fluorenoyl carbapenems with excellent activity against MRSA, abstr. F50, p. 126. *In* Abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
20. **Sentochnik, D. E., G. M. Eliopoulos, M. J. Ferraro, and R. C. Moellering, Jr.** 1989. Comparative in vitro activity of SM7338, a new carbapenem antimicrobial agent. Antimicrob. Agents Chemother. **33:**1232–1236.
21. **Sundelof, J. G., J. J. Jackson, C. J. Gill, W. J. Cleare, N. Walker, K. M. White, and H. Kropp.** 1994. *In vivo* activity of a prototype carbapenem antibiotic in localized and systemic MRSA murine models, abstr. F64, p. 127. *In* Abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
22. **Williamson, R., C. LeBouguénec, L. Gutmann, and T. Horaud.** 1985. One or two low affinity penicillin-binding proteins may be responsible for the range of susceptibility of *Enterococcus faecium* to benzylpenicillin. J. Gen. Microbiol. **131:**1933–1940.