

1 β -Methylcarbapenem antibiotics

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Introduction

In 1976, a new potent, broad spectrum carbapenem antibiotic, thienamycin, was isolated from the fermentation of *Streptomyces cattleya* by Merck scientists (1). Thienamycin not only has a remarkable novel structure in that it differs from the penam nucleus of the penicillins in having a carbon atom replacing a sulfur atom at the 1 position and in having an unsaturated bond between atoms 2 and 3 in the 5-membered ring, it also contains a unique hydroxyethyl side chain in the *trans* (α) configuration at position 6 (2). This new class of carbapenem antibiotics has been extensively studied since the discovery of thienamycin (Fig. 1). Although thienamycin possesses high potency against an unusually broad spectrum of bacteria, it is so chemically unstable, both in the solid state and in a concentrated solution, that it has not been used clinically. Semisynthetic structural modifications of thienamycin led to *N*-formimidoyl thienamycin, imipenem (3). However, imipenem when subjected to hydrolysis by dehydropeptidase-I (DHP-I) was nephrotoxic when administered alone (4). This problem was solved by coadministration of an efficient inhibitor of DHP-I, cilastatin. Imipenem/cilastatin was launched in 1987 in Japan as the first carbapenem antibiotic (5, 6). The second carbapenem antibiotic, panipenem/betamipron, was launched in 1993 in Japan by Sankyo. Panipenem differs chemically from imipenem in having a *N*-acetimidoylpyrrolidinylthio side chain at the C-2 position (7) and betamipron differs in that it is not an inhibitor of DHP-I but an organic anion transport inhibitor preventing renal dysfunction by blocking active tubular secretion of the antibiotic (8).

1 β -Methylcarbapenems, without coadministration of cilastatin or betamipron, have been extensively studied recently because of their high potency. The purpose of

this review is to focus on parenteral and oral 1 β -methylcarbapenem antibiotics.

Antibacterial targets

β -Lactam antibiotics exhibit their activity by inhibiting bacterial cell wall synthesis. For an antibiotic to inhibit microorganisms, the antibiotic must reach its target site. Gram-positive species have an outer surface structure which is relatively permeable to many substances since they have no outer membrane and their cell wall consists of 20-30 loosely connected strands of peptidoglycan, which is composed of alternating sequences of *N*-acetylglucosamine and *N*-acetylmuramic acid, extending in one direction by β -1,4-linkage, cross-linked by short peptides in a second direction. In Gram-positive bacteria, β -lactamases are excreted as exoenzymes and destroy the β -lactams. β -Lactams not degraded by β -lactamase diffuse through the cell wall and bind to penicillin-binding proteins (PBPs) which are located on the cytoplasmic membrane and inhibit peptidoglycan synthesis. Conversely, Gram-negative bacteria possess a complex lipopolysaccharide outer membrane which contains various pores through which hydrophilic substances can pass to reach the periplasmic space that exists between the outer cell wall and the cytoplasmic membrane. β -Lactams cannot diffuse through the tightly structured phospholipid areas and diffuse only through porin channels. β -Lactams not degraded by β -lactamase in the periplasmic space bind to target PBPs and inhibit peptidoglycan synthesis. Some differences exist among the carbapenems in their affinity for PBPs.

Parenteral carbapenems

1 β -Methylcarbapenems

Shih *et al.* reported on the first 1 β -methylcarbapenem derivatives (9), and also synthesized 1 β - and 1 α -methyl thienamycin (10). 1 β -Methyl thienamycin was biologically more active than thienamycin against Gram-negative bacteria and, more significantly, it was highly resistant to enzymic hydrolysis of DHP-I. On the other hand, 1 α -methyl thienamycin was somewhat resistant to DHP-I hydrolysis but its antibacterial activities were greatly

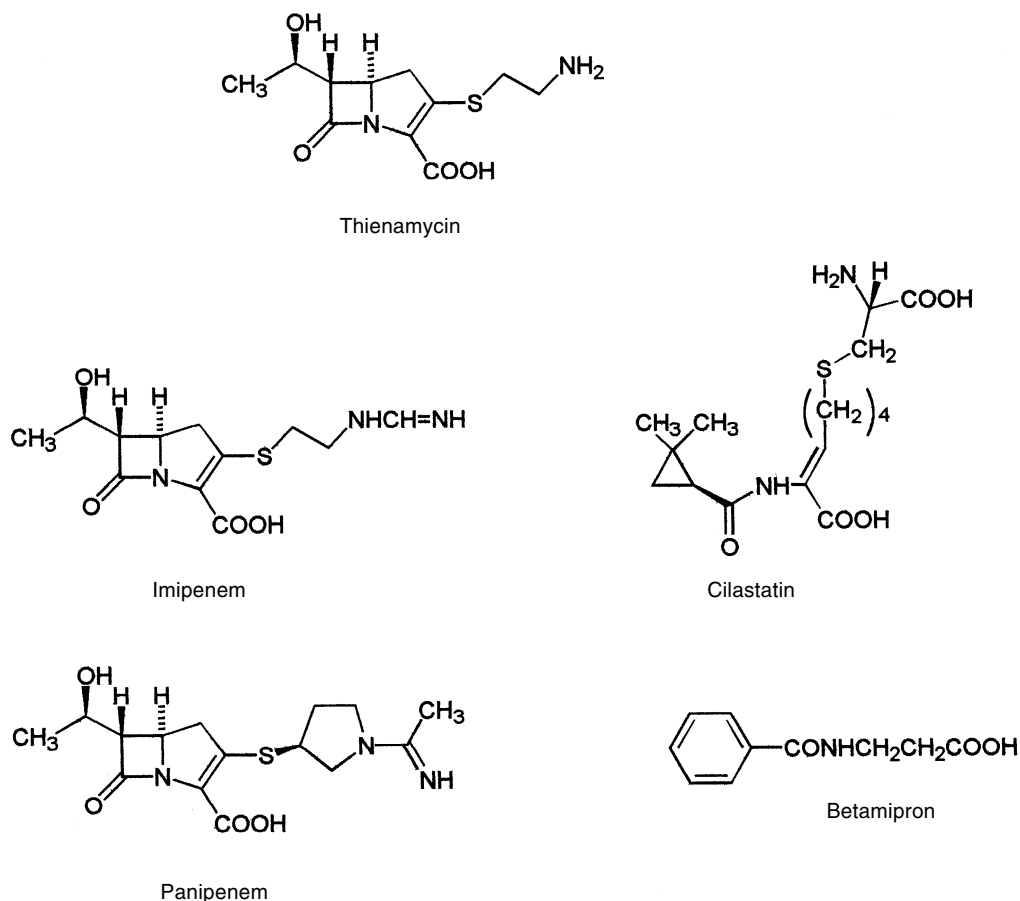


Fig. 1. Structures of thienamycin, imipenem, cilastatin, panipenem and betamipron.

decreased (11). These findings opened up new opportunities to design a variety of metabolically stable 1 β -methylcarbapenem antibiotics (Fig. 2), among them, L-646,591. The ratio of DHP-I susceptibilities of L-646,591 and imipenem in comparison to thienamycin (1.0) were 0.026 and 0.90, respectively. Relative *in vitro* antibacterial potency was improved against Gram-negative bacteria, including *Pseudomonas aeruginosa*, compared with that of imipenem, but it had slightly weaker activity against Gram-positive bacteria than imipenem. However, L-646,591 showed nephrotoxicity.

Many research centers have focused their attention on the synthesis of nonnephrotoxic 1 β -methylcarbapenem derivatives (Fig. 3). Sunagawa *et al.* reported meropenem (SM-7338), which differs in having a dimethylcarbamoilpyrrolidinythio side chain attached at the C-2 position (12). Meropenem was more active than imipenem against Gram-negative bacteria, including *Escherichia coli* and *P. aeruginosa*, whereas it was slightly less active than imipenem against Gram-positive bacteria (13). Meropenem was considerably more resistant to human DHP-I than imipenem. The pharmacokinetics of meropenem in healthy volunteers were comparable to those of imipenem/cilastatin (14). The urinary recovery of meropenem (69%) was similar to that of the

imipenem/cilastatin combination (70%), but considerably greater than that of imipenem alone (5.5-42.5%). Meropenem was launched in Japan as the first 1 β -methylcarbapenem antibiotic by Sumitomo Pharmaceuticals.

Biapenem, a new 1 β -methylcarbapenem having a bicyclic triazolium moiety attached to the sulfur at the 2-position, was developed by Lederle Japan (15). Biapenem was more active than imipenem against most Gram-negative bacteria, including *Enterobacteriaceae*, *P. aeruginosa* and *Acinetobacter* spp., but slightly less active than imipenem against Gram-positive bacteria, including staphylococci and streptococci (16-20). Biapenem is also resistant to DHP-I and thus was able to be developed without coadministration of a DHP-I inhibitor (21).

Simada and Kawahara reported human pharmacokinetic parameters of 1-H carbapenems (imipenem/cilastatin and panipenem/betamipron) and 1 β -methylcarbapenem (meropenem and biapenem) and susceptibility to human kidney DHP-I (22). Clearly, some difference between 1-H carbapenems and 1 β -methylcarbapenems was found in the DHP-I activity, but there was no significant difference in the pharmacokinetic parameters AUC, CL_{tot} , $t_{1/2}$ and MRT, except urinary recovery after adminis-

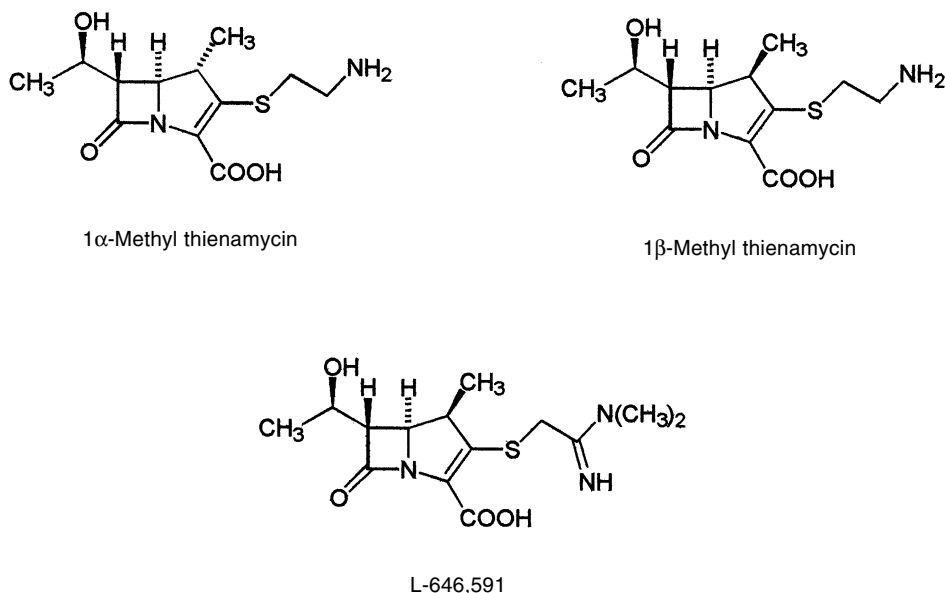


Fig. 2. Structures of 1α-methyl thienamycin, 1β-methyl thienamycin and L-646,591.

tration of these compounds to humans. The plasma half-lives of imipenem/cilastatin, panipenem/betamipron, meropenem and biapenem were 0.97, 0.90, 0.93 and 0.96 h, respectively. It was clear that imipenem and panipenem needed to be coadministered with cilastatin and betamipron, respectively, in order to reduce renal toxicity, but coadministration was unnecessary with meropenem and biapenem.

From the standpoint of antibacterial activity, 1β-methylcarbapenems were generally more active against Gram-negative bacteria and slightly less active against Gram-positive bacteria compared with 1-H carbapenems. Carbapenems such as imipenem/cilastatin, panipenem/betamipron and meropenem, which are on the market today, have potent activity against *P. aeruginosa*. However, in recent years the emergence of imipenem-resistant *P. aeruginosa* strains has been observed. Most of these strains lack the *oprD* channel, which facilitates the diffusion of imipenem into the cell (23, 24). Moreover, it has been shown that overproduction of *oprM* caused by *nalB* mutation is associated with higher levels of resistance to meropenem in *P. aeruginosa* (25).

BO-2727 had inhibitory activity against imipenem- and meropenem-resistant *P. aeruginosa* strains (26, 27). Against methicillin-resistant staphylococci, BO-2727 was the most active among the three antibiotics (imipenem, meropenem and biapenem) but slightly less active than imipenem against methicillin-susceptible staphylococci. BO-2727 had activity comparable to those of imipenem and biapenem against *Enterobacteriaceae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, although it was less active than meropenem against these species. Pharmacokinetic parameters of BO-2727 were reported in a phase I study (28). The plasma half-life ($t_{1/2}$) of BO-2727 (dose 250 mg) was 1.4 h and the mean urinary recovery rate within 24 h was approximately 73% (28).

Interestingly, the mean $t_{1/2}$ of BO-2727 was longer than those of the other four carbapenems.

The carbapenem S-4661, which has a 5-(sulfamoylaminomethyl)-pyrrolidin-3-ylthio group at the C-2 position, has been synthesized and its biological properties have been evaluated (29, 30). S-4661 exhibited better antibacterial activity than meropenem against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* SR3131. Against Gram-negative bacteria, S-4661 showed comparable activity to that of meropenem. The pharmacokinetic profile of S-4661 in the phase I study was similar to that of meropenem (31).

A novel long-acting carbapenem, L-749,345 (ZD-4433), has been reported by Merck scientists (32). The activity of L-749,345 was slightly less than that of imipenem against Gram-positive bacteria and was superior to that of imipenem against Gram-negative bacteria, with the exception of *P. aeruginosa*. Against respiratory tract bacterial pathogens, especially *H. influenzae* and *M. catarrhalis*, L-749,345 was more active than imipenem (33). Also, against broad- and extended-spectrum β-lactamase (BDSβLs and ESβLs)-producing clinical isolates of *E. coli* and *Klebsiella pneumoniae*, its activity exceeded that of third- and fourth-generation cephalosporins (34). The plasma half-life ($t_{1/2}$) of L-749,345 was approximately 4.5 h after administration of a single dose (1000 mg i.v.) and the urinary recovery was 37% within 48 h (35). From these results, 1000 mg once a day was the recommended clinical dose of L-749,345.

Biapenem, BO-2727, S-4661 and L-749,345 are all under clinical trials and other 1β-methylcarbapenems are undergoing preclinical assessment.

A new antipseudomonal carbapenem, DX-8739, having an (S)-5-amino-2-hydroxypentanoyl moiety added onto the nitrogen of the piperazine ring of the C-2 side

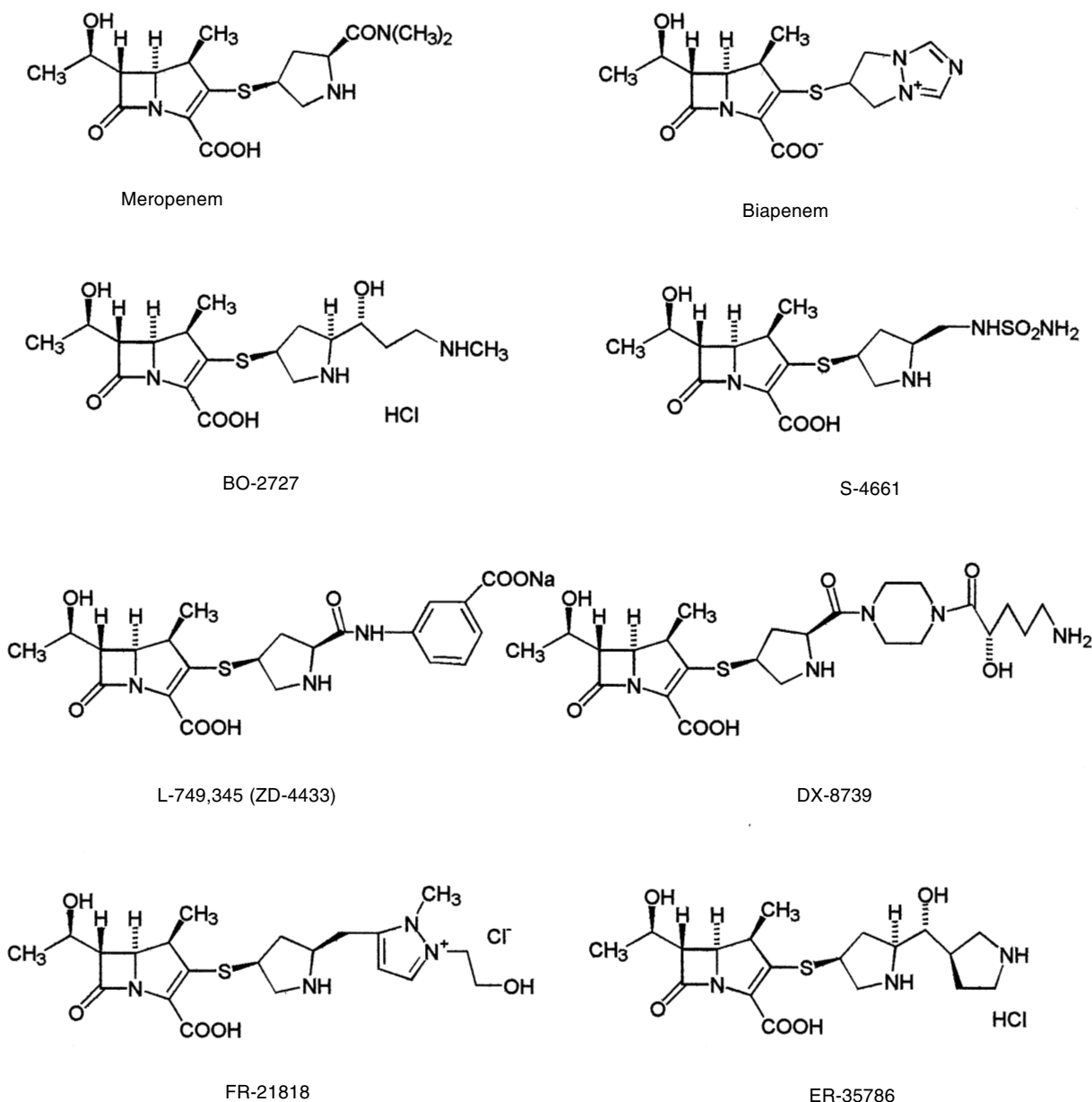


Fig. 3. Structures of parenteral 1 β -methylcarbapenems.

chain, has been reported (36-38). The activity of DX-8739 against *P. aeruginosa* was superior to that of imipenem and meropenem. DX-8739 and meropenem inhibited 33 and 27% of imipenem-resistant *P. aeruginosa* strains, respectively. DX-8739 also inhibited 30% of the meropenem-resistant population.

FR-21818 is another new 1 β -methylcarbapenem containing a unique pyrazolomethylpyrrolidine side chain at the C-2 position (39). *In vitro* antibacterial activity, stability to renal DHP-I and urinary recovery of FR-21818 were compared to those of meropenem and biapenem. FR-21818 showed superior activity against *S. aureus* strains, although it was marginally weaker than meropenem

against Gram-negative bacteria with the exception of *P. aeruginosa*. The DHP-I stability of this compound was between those of meropenem and biapenem. The urinary recovery of FR-21818 in mice after subcutaneous administration was 68.9%.

ER-35786 is a modified structure of BO-2727 (40, 41). The *in vitro* activity of ER-35786 against anaerobes was slightly less than that of meropenem and was similar to that of BO-2727. The DHP-I stability of ER-35786 was closer to that of biapenem than to that of meropenem. The urinary recovery of ER-35786 (10 mg/kg i.v.) in laboratory animals was 50.4% in mice, 38.8% in rats, 78.4% in dogs and 47.7% in cynomolgus monkeys within 6 h.

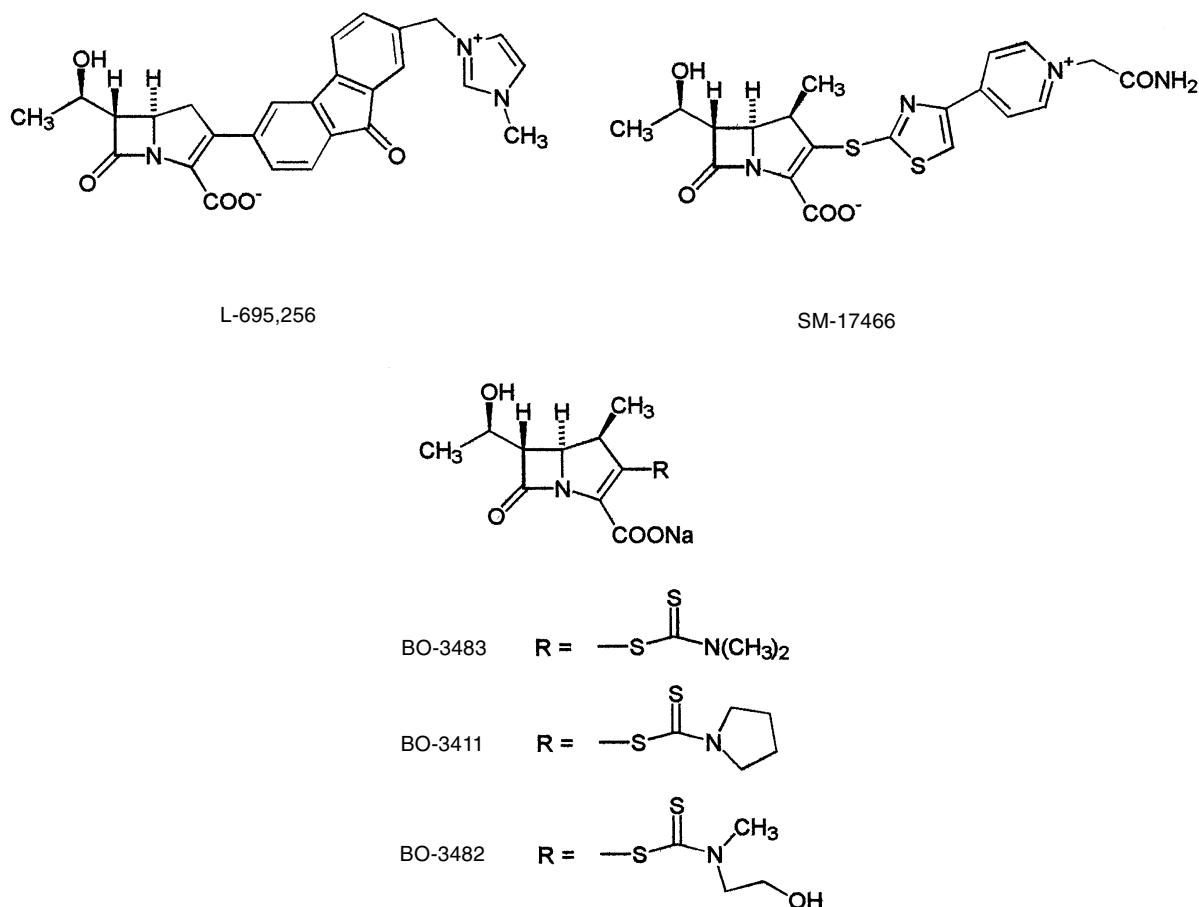


Fig. 4. Structures of anti-MRSA carbapenems.

These preliminary biological evaluations of this new agent showed a broad spectrum of activity and excellent stability to DHP-I.

Anti-MRSA carbapenems

Carbapenem antibiotics, *e.g.*, imipenem, panipenem and meropenem, possess an extremely broad spectrum of activity and are used clinically for the treatment of severe infections. However, they lack efficacy against methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant enterococci because they have low affinity for the PBPs of these organisms. In the past several years, the rapid emergence of bacterial resistance, including MRSA, to antibiotics has been observed (42, 43). At present, the only drugs effective for multiply resistant MRSA infections are vancomycin, and arbekacin in Japan. Worldwide, vancomycin is the most popular treatment for MRSA. Moreover, with the recent increase in the use of vancomycin for MRSA infections and colitis due to *Clostridium difficile*, multiply resistant *Enterococcus faecium* has emerged. Research to discover new antibacterial agents with activity against MRSA continues today. In the

field of carbapenem antibiotics, Merck scientists found a furorenyl 1-H carbapenem, L-695,256 (44-46), which possessed high affinity for the PBP2a (PBP2') and recently they reported the synthesis of benzothiazolylthio 1 β -methylcarbapenems (47). L-695,256 has higher *in vitro* and *in vivo* potency than vancomycin against MRSA, although this compound has the same level of activity against *E. faecium* as vancomycin (Fig. 4).

The *in vitro* and *in vivo* antibacterial activities of the 1 β -methylcarbapenem, SM-17466, were evaluated against a wide range of clinical isolates and compared to the activities of meropenem, imipenem, vancomycin and arbekacin (48). The MIC₉₀s of SM-17466, meropenem, imipenem, vancomycin and arbekacin were 3.13, 50, 100, 1.56 and 3.13 $\mu\text{g/ml}$, respectively. The *in vivo* efficacy of SM-17466 against methicillin-resistant strains (2 strains) was equal to that of vancomycin and arbekacin for one strain and one-third that of vancomycin for the second strain.

Another series of anti-MRSA 1 β -methylcarbapenems having a dithiocarbamate moiety has been investigated (49). BO-3483 and BO-3411 exhibited MICs ranging from 3.13 to 6.25 $\mu\text{g/ml}$, respectively, against high-level MRSA. BO-3482, having a *N*-(2-hydroxyethyl)-*N*-methylaminothio-

Oral 1 β -methylcarbapenems

A novel orally active 1 β -methylcarbapenem, CS-834, is also undergoing clinical trials. The structure-activity

relationships of CS-834 and related compounds have been reported (54, 55). The antibacterial activity of the parent compound of CS-834, R-83201, was superior to that of cefpodoxime (56) against Gram-positive and Gram-negative bacteria, and was almost equal to that of the parenteral carbapenems imipenem and panipenem, except against *P. aeruginosa*. GV-104326, seems to be inferior to R-83201 in antibacterial activity against Gram-negative bacteria. The effect of cilastatin on urinary recovery and the DHP-I degradation of related carbapenems including 1-H carbapenem of R-83201 were elucidated. The urinary recovery of R-83201 after s.c. administration in mice was 75%, reflecting higher resistance against DHP-I. Conversely, the urinary recovery of the 1-H analog was only 8%, which was in accordance with the fast degradation by DHP-I. CS-834 showed good oral absorption in mice and dogs and excellent therapeutic efficacy against systemic infections in mice. It was also highly effective especially against infections caused by resistant strains of bacteria to which oral cephalosporins had been inactive (57, 58). The chemical stability of CS-834, its 1-H derivative and cephalosporin esters which have the same ester promoiety were compared with each other (59). Interestingly, contrary to the conventional view that carbapenems are unstable even under neutral conditions, both carbapenems showed higher stability than the cephalosporins. CS-834 was

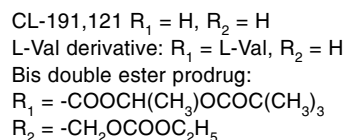
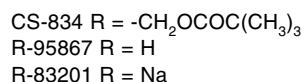
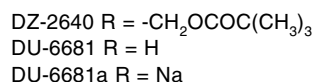
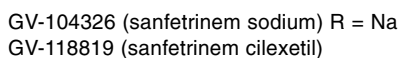


Fig. 5. Structures of oral carbapenems.

more stable than the 1-H analog, probably due to the enhancing contribution of the 1 β -methyl group which sterically protects the β -lactam ring against hydrolysis. Pharmacokinetics in laboratory animals and results of a phase I study have also been reported (60, 61). CS-834 is now in phase II clinical trials.

Another series of novel oral 1 β -methylcarbapenems having a bicyclic imidazole ring as a side chain at the C-2 position has been synthesized (62). Among these, DU-6681a had a potent antibacterial activity and broad antimicrobial spectrum but was ineffective against *P. aeruginosa* (63, 64). Among the prodrug esters of DU-6681, the pivaloyloxymethyl ester, DZ-2640, showed good absorption in rats after oral administration. Urinary recovery of the parent compound after single oral administration of DZ-2640 to rats was 24.6%.

Another novel 1 β -methylcarbapenem reported, CL-191,121, has an amino methyl THF moiety attached to the sulfur at the C-2 position (65). CL-191,121 had a broad spectrum of activity against Gram-positive and Gram-negative organisms, comparable to or better than that of imipenem, but displayed only moderate antipseudomonal activity. The effective oral dose (ED₅₀) of CL-191,121 was more than 10-fold higher than the effective subcutaneous dose. In order to improve oral absorption, the syntheses of peptidic prodrug and bis double prodrug of CL-191,121 were attempted. Among the L-amino acid derivatives, the L-Val derivative of CL-191,121 demonstrated the best oral activity (66). On the other hand, among bis double ester derivatives, the pivaloyloxy-1-ethyl ester derivative had oral activity that was as good as that of the L-Val derivative of CL-191,121 (67).

Conclusions

Since the discovery of thienamycin, carbapenems have received extensive attention because of their potent antibacterial activity and their wide spectrum of activity against Gram-positive and Gram-negative bacteria. In particular, 1 β -methylcarbapenem antibiotics have enhanced metabolic stability to renal dehydropeptidase-I compared with 1-H carbapenems. 1 β -Methylcarbapenem antibiotics can be administered without coadministration of cilastatin or betamipron. However, in recent years, new antibiotic-resistant strains such as imipenem- and/or meropenem-resistant *P. aeruginosa* have been isolated from patients worldwide. This requires the development of a new 1 β -methylcarbapenem antibiotic devoid of cross-resistance with other antimicrobial agents already in use. The increase in the number of isolated MRSA strains is also a serious problem in clinical practice.

Present research is focused on the discovery of a potent anti-MRSA carbapenem antibiotic as an alternative to vancomycin. The recent development of new oral 1 β -methylcarbapenem antibiotics exhibiting no cross-resistance with oral cephalosporins and new quinolones will be an exciting development in the field of β -lactam antibiotics. A better understanding of the bacterial resis-

tance mechanism and rational drug design based on structure-activity relationships will be essential to finding a new carbapenem antibiotic.

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