

THE STRUCTURAL ASPECTS OF CARBAPENEM ANTIBIOTICS

Makoto Sunagawa* and Akira Sasaki

Sumitomo Pharmaceuticals Research Center

1-98, Kasugadenaka 3-chome, Konohana-ku, Osaka 554-0022, Japan

Abstract-The discovery of thienamycin in 1976 caused much synthetic research effort to be concentrated on carbapenem antibiotics, by many groups. To date, two carbapenems, which need to be coadministered with other drugs, and then a new generation carbapenem, which could be utilized as a single agent, were developed for clinical use based on the progress of synthetic chemistry. Today, attention has been focused on the development of next generation carbapenem antibiotics. These trends of the carbapenem antibiotics developed in last quarter century are reviewed from a viewpoint of their chemical structures.

INTRODUCTION

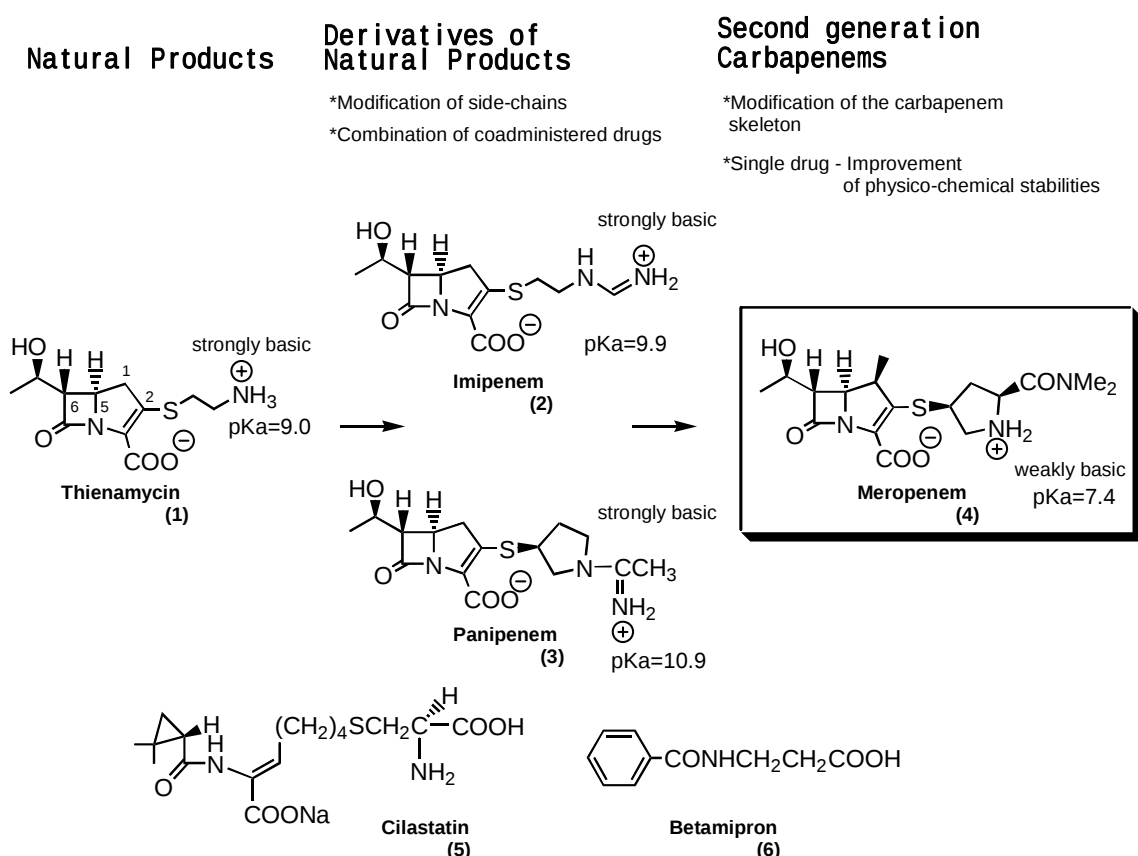
The discovery of thienamycin (**1**) (**Figure 1**), the first naturally occurring carbapenem antibiotic reported by the Merck group in 1976,¹ made an impact in the long history of β -lactam antibiotics, the major of which area had been occupied by penicillin and cephalosporin antibiotics.

Compound (**1**) has a novel chemical structure and shows excellent antibacterial activity against not only the strains sensitive penicillin and/or cephalosporin antibiotics but also the resistant ones. However, it was clear that the development of **1** itself was difficult owing to its shortcomings, such as poor chemical and biological stability, nephrotoxicity and neurotoxicity, for clinical use.

During the last quarter century, extensive works on the development of carbapenem antibiotics for clinical use were performed by researchers in a variety of fields, mainly by two methods. One involved the searching of new naturally occurring carbapenems. From this work, more than fifty carbapenems have been isolated. But, unfortunately none of them has proved to be superior to **1** in the antibacterial profile. The other involved so-called "lead optimization", of which the lead compound was a natural-origin carbapenem, especially **1**, based on synthetic and medicinal chemistry. Efficient synthetic methodologies towards carbapenem derivatives were established and a variety of carbapenems were synthesized. Structure-activity relationships (SARs) of carbapenems, concerning

the antibacterial activities, chemical stability, biological stability (susceptibility against renal dehydropeptidase-I, DHP-I) and also side effects, were widely investigated.²

Figure 1



As a result, three carbapenem antibiotics have been introduced for clinical use to date. The first carbapenem antibiotic, imipenem (2),³ was launched in the middle of the 1980s as a drug coadministered with cilastatin (5), which shows the dual function of inhibiting DHP-I and decreasing the nephrotoxicity. Another was panipenem (3),⁴ which is closely related to 2, structurally and biologically, and was developed mainly in Japan as a drug coadministered with betamipron (6), an inhibitor against the organic anion transportation, that decreased the nephrotoxicity. Both of the first generation carbapenems had the natural carbapenem skeleton and a strongly basic (cationic) group in the C2 side-chain similar to 1.

On the other hand, the new generation carbapenem, meropenem (4),⁵ having the 1 β -methylcarbapenem skeleton and a significantly less basic group in the C2 side-chain, had arrived as a world prominent drug in the middle of the 1990s. In particular, 4 was the first drug which was developed as a single agent without the need of any coadministered drugs due to the successful achievement of decreasing not only the nephrotoxicity but also neurotoxicity and also an improved

antibacterial profile.

In the development of these carbapenem antibiotics including 2, 3 and 4, the synthetic approach played a very important role, although the semi-synthetic procedure starting from natural products was widely applied in the cases of penicillin and cephalosporin antibiotics. The progress of synthetic studies has strongly propelled development. The synthetic chemistry enabled varied structure-activity relationship (SAR) studies to be achieved thoroughly and also a practical sample supply for toxicological studies, clinical studies and so on.

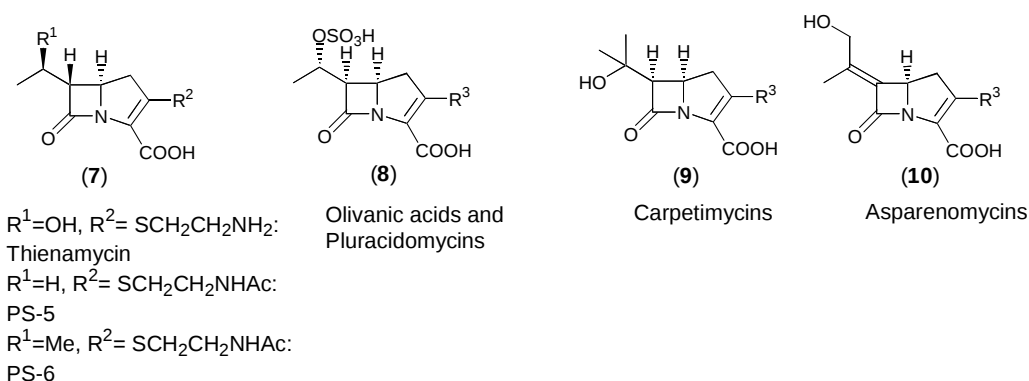
As for the synthetic chemistry of carbapenem antibiotics, many reviews have already been reported.⁶ However, the history of carbapenem antibiotics focused on their structural transition in the development of carbapenem antibiotics has not yet been reviewed.

In this article,[†] we try to overview the research trend of carbapenem antibiotics development in these 25 years from a viewpoint of their chemical structures. Future trends are also briefly discussed.

The Discovery of naturally occurring carbapenems

After reporting thienamycin's discovery, the searching programs of new natural-origin carbapenems were extensively performed by several research groups.⁷ It was interesting that a lot of new carbapenem antibiotics were isolated almost simultaneously, in a relatively short period. To date, a number of thienamycin derivatives and other related carbapenems were isolated from natural sources.^{2a,2d} Those included epithienamycins, olivanic acids, carpetimycins, asprenomycins, pluracidmycins, PS series and so on.

Figure 2



All of these have the carbapenem skeletons substituted both on C2 and C6. In general, the C2 side-chain is cysteamine or its derivatives modified by acylation of the amino group, oxidation of the sulfur atom to sulfoxide, dehydrogenation of CH_2CH_2 etc., and the substituent on C6 was a $C_2\sim C_3$ alkyl moiety, such as ethyl, 1-

hydroxyethyl, isopropyl, and 1-hydroxyisopropyl.

Although the novel structures of all naturally occurring carbapenems are scientifically interesting, the first carbapenem (**1**) was the most attractive from a viewpoint of the antibacterial profile because it has the most potent antimicrobial activity. Chemical modification on the natural-origin carbapenems had also been carried out. However, those were rather limited because of the poor sample supply, from natural sources, due to the low abundance and the physicochemical unstability. The natural product chemistry of carbapenem antibiotics afforded a lot of valuable findings for the development of carbapenem antibiotics. Among them, *N*-formimidoylthienamycin (imipenem, **2**),³ the physicochemical stability of which was improved without losing the antibacterial activity of **1**, was notable since it was the only compound successfully introduced into the clinic.

The limitation of sample supply by fermentation methods forced the main stream of the development studies towards direct synthetic approaches at a relatively early stage.⁸

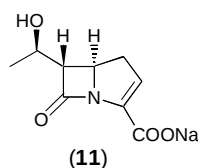
Establishment of carbapenem synthesis (1977-1983)

Carbapenem antibiotics, which had not only excellent antibacterial activity but also a unique chemical structure, were quite attractive targets for chemists to investigate synthetic methodologies and/or development of carbapenem derivatives for clinical use. Accompanied with Merck's selection of imipenem (**2**) as a clinical candidate, synthetic studies towards **2** were widely performed.⁹ Afterwards it was launched in 1984 as a drug coadministered with cilastatin (**5**), that improved the biological stability against DHP-I and decreased the nephrotoxicity of **2**.¹⁰ Thus **2** was a direct result of "lead optimization", *vide supra*. Many other research groups throughout the world also started to study the synthesis of carbapenems. Thus, the synthetic chemistry of carbapenems including efficient synthetic routes to the carbapenem skeleton and facile, methods of introducing the C2 side-chain, etc. were established over a few years.

A variety of carbapenem derivatives were synthesized based on the progress of synthetic chemistry.⁶ These could be divided into two categories from the origin of the research objectives. One included a series of natural products and designed derivatives for the lead optimization of natural carbapenems, especially **1**. The other contained mimics or simplified derivatives of natural carbapenems which were derived mainly from the synthetic chemistry of carbapenems.

The main results are given chronologically: Christensen *et al.* reported the synthesis of **1**, **2**, and also a C2 non substituted derivative (**11**), which showed moderate antibacterial activity.¹¹

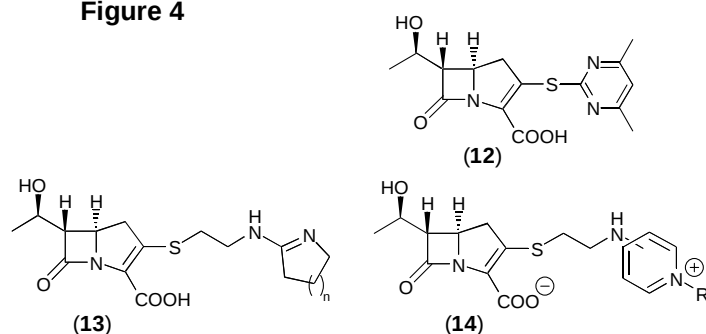
Figure 3



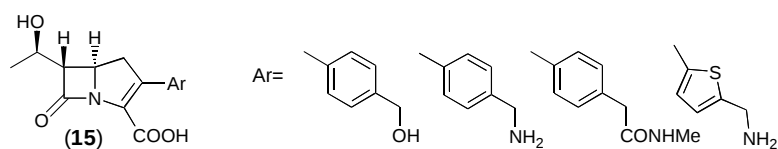
In this work, it was suggested that the chemical modification of the side-chain at C2 was one of the quite attractive approaches in the lead optimization of carbapenems. Following this report, synthetic efforts by many research groups were directed towards thorough chemical modification of the C2 side-chain using newly established effective synthetic methodologies of skeleton construction and mercapto-side-chain introduction into C2.

The introduction of not only the closely related mimics to cysteamine but also the new type of substituents such as alkylthio, phenylthio, heteroarylthio group was achieved. Baxter *et al.* reported the synthesis of a 2-pyrimidinylthio derivative as an olivamic acid analogue.¹² The synthesis of thienamycin derivatives having quaternary heterocyclammonium moiety in C2 side-chain was reported by Hannah *et al.*¹³ This was the first synthesis of the carbapenem containing a quaternary ammonium moiety, which was popular in the field of cephalosporin antibiotics. This approach became a major trend, as in the field of the cephalosporin antibiotics.

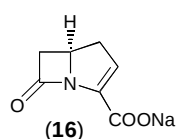
Figure 4



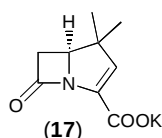
One of the results in the studies of cysteamine mimics, panipenem (**3**), which was launched in 1993 as the second carbapenem antibiotic coadministered with a reducer of nephrotoxicity, betamipron (**6**) in Japan, was reported at International Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in 1982 by the Sankyo group.⁴ The extension of the modification studies on C2 reached to the non-natural type of carbapenems which had a C-C bond instead of a C-S bond for the connection of the C2 side-chain of carbapenems.¹⁴ It was shown that those carbapenems had a slightly different antibacterial profile compared with the carbapenems containing the C-S bond.

Figure 5

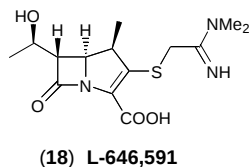
As for the C6 substituent, it was noted that a simple carbapen-2-em-3-carboxylic acid (16) itself still possessed moderate antibacterial activity, although the susceptibility against β -lactamases was higher compared with the 1-hydroxyethyl derivative (11).^{2a,11}

Figure 6

Therefore, chemical modification at the C6 position was undertaken, but was limited due to the difficulty of synthesizing effectively such derivatives. Some of the derivatives, however, including C6 non substituted carbapenems, resulted from the methodology development of the carbapenem skeleton synthesis, were prepared and evaluated biologically. Among them, the following report was notable because their concept of modification was novel.¹⁵ The 1,1-dimethylcarba-2-penem derivative (17) exhibited considerable antibacterial activities.

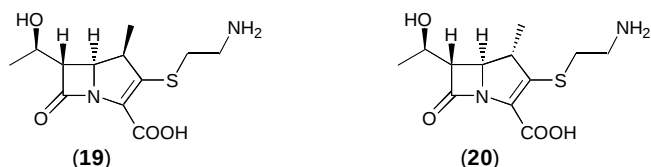
Figure 7

At ICAAC in 1983, the epoch-making report concerning the C1-substituent of carbapenems was presented by the Merck group.^{16,17}

Figure 8

That was, the synthesis and biological comparison of 2,6-disubstituted carbapenem and 1,2,6-trisubstituted carbapenem derivatives were presented and it was shown that the introduction of 1 β -methyl group improved significantly both the physicochemical stability and stability against DHP-I (the biological one) without losing the antimicrobial activities.

Figure 9



Afterwards, the 1 β - and 1 α -methylthienamycins were also synthesized and biologically tested.¹⁸ In particular, the fact that the 1 β -methyl group but not the 1 α -methyl group increased both stabilities, was confirmed.

In this first era (1977-1983) of the carbapenem development by synthetic approaches, most of the important findings and knowledge that directed the research trends afterwards were clarified, including the importance of the C6 substituent for the stability against β -lactamases, the necessity of the cationic moiety in a C2 side-chain for the antipseudomonal activity, and the merit of 1 β -methyl introduction.

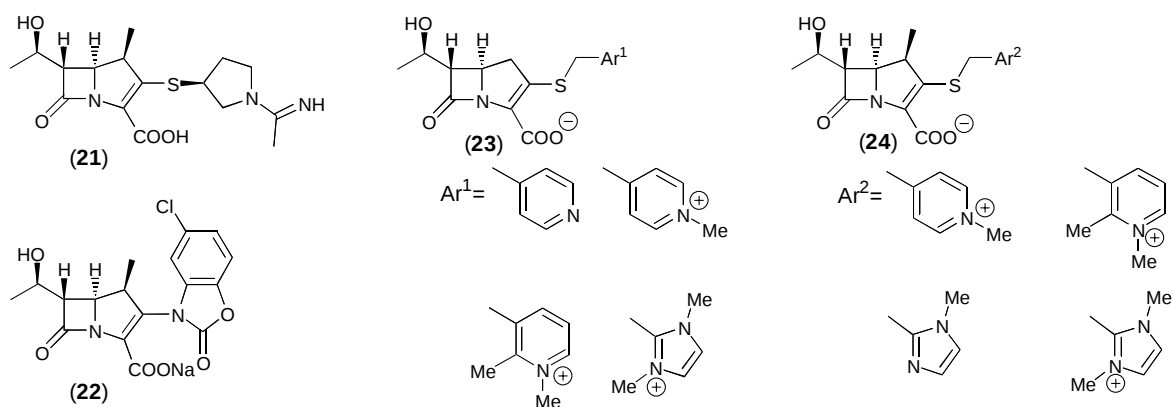
The evolution of the synthetic chemistry of carbapenems (1984-1989)

Like the success of establishing the industrial chemical process to imipenem (2) by the Merck group,⁹ the synthetic chemistry of carbapenems grew as a powerful tool to proceed with development studies of carbapenem antibiotics in clinical use. The rapid progress in synthesis was reflected in the increased speed at which medicinal chemistry of carbapenems could be carried out.

The modifications of the C6 side-chain were extensively continued, and a variety of carbapenem derivatives having unique C2 side-chains connected by C-C or C-S bonds were reported.

In this period of carbapenem history much attention was focused on the merit of the introduction of the C1-substituent. Particularly, 1 β -methylcarbapenems were widely synthesized.

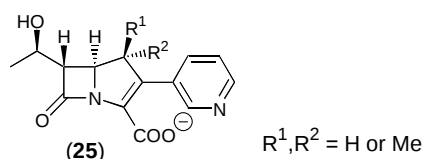
Figure 10



It should be noted that extensive efforts of many synthetic chemists throughout the world concentrated on the development of effective methodologies of 1 β -methylcarbapenem synthesis simultaneously.⁶ⁱ The synthesis of 1 β -methylcarbapenem derivatives which had interesting C2 side-chains resulting from C2 side-chain optimization studies in carbapenems were successively reported (**Figure 10**).^{19,20}

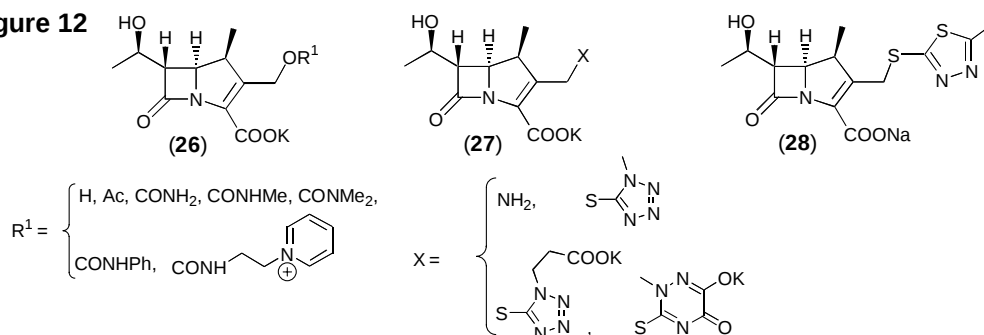
The application to the non-natural carbapenems having a C-C bond at the C2 position was also tried.

Figure 11



It is interesting that the introduction of 1 β -methyl group caused diminution of the biological stability in the case of compound (25) and the limitation of the 1 β -methyl substituent was shown for the first time.²¹ Other types of compounds (26~28) were also synthesized.²²⁻²⁴

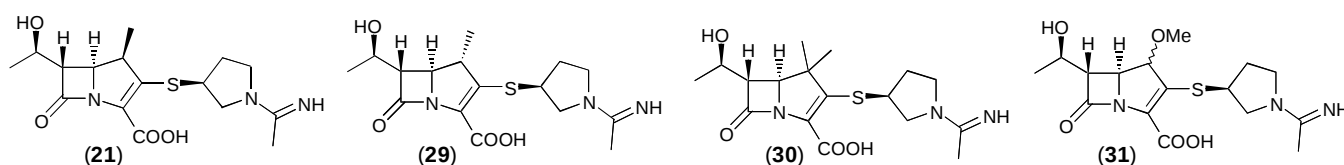
Figure 12



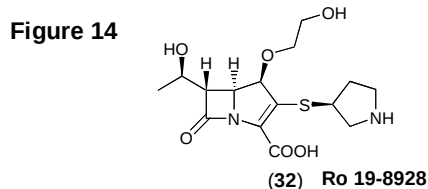
New effective substituents at C1, instead of the 1 β -methyl group, were extensively explored. Several research groups tried to introduce a hetero atom at the C1 position as well as the 1 β -methyl group. Concerning alkoxylation, the following examples were found.²⁵⁻²⁸

The Sankyo group reported the synthesis of 1-methoxypanipenem (31) together with those of other 1-methylated analogs.²⁵

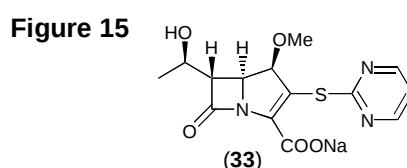
Figure 13



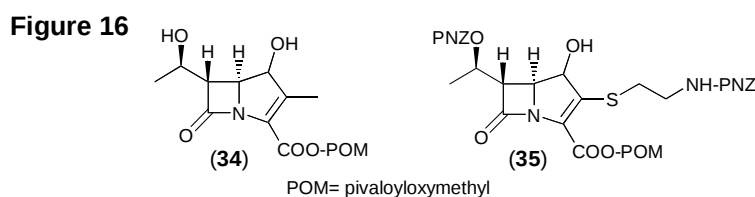
The Roche group reported the systematic synthetic study of 1-alkoxy derivatives. Among them, **32** showed considerable activity against *Pseudomonas aeruginosa*.²⁶



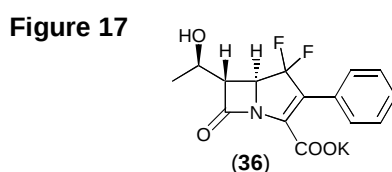
Nagao *et al.* reported the stereoselective synthesis of 1 β -methoxy derivative (**33**).²⁷



1-Hydroxythienamycin could not be isolated due to its low chemical stability.²⁸



The Merck group reported the introduction of fluorine atoms at the C1 position.²⁹

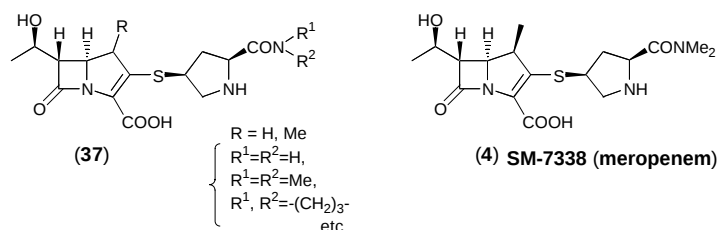


The characterization of 1,1-difluorocarbapenem (**36**) could only be performed by its UV spectrum due to its low chemical stability and the biological properties were unclear.

Among those efforts, we reported **SM-7338** (meropenem, **4**) as a development candidate at ICAAC in 1987.⁵ We conducted the rational design of a new carbapenem antibiotic, focused on the development of effective and safe carbapenem antibiotics, of which the profile was generally the most prominent advantage of β -lactam antibiotics compared with other types of antibacterial agents. The detailed SAR studies between structural/physicochemical properties and biological activities including antibacterial activities, nephrotoxicity and neurotoxicity in a series of 1 β -methylcarbapenem compounds having 2,4-

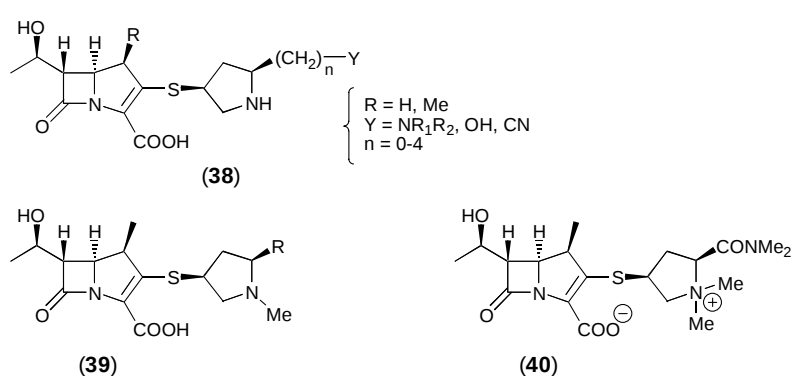
disubstituted pyrrolidine side-chain at C2, afforded many useful findings.³⁰⁻³³

Figure 18



The introduction of a methyl group on the nitrogen atom and the insertion of a methylene spacer enhanced the stability against DHP-I synergetically.

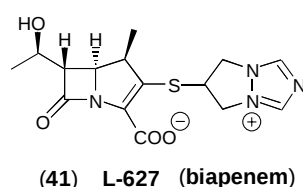
Figure 19



In particular, the important roles of the basicity of the C2 side-chain of carbapenem in many biological activities were clarified. As a result, it was confirmed that meropenem (4) had a satisfactory target profile by means of such SAR studies. In fact, meropenem was the first developed drug in the world in clinical use without any coadministered drug in middle of 1990s. Afterwards, the studies of meropenem-type carbapenems, which had the 2, 4-disubstituted pyrrolidine moiety, became one of the big areas for the development of carbapenem antibiotics as described later.

L-627(biapenem, 41), that was under development, was reported by the Lederle group at ICAAC in 1989.³⁴ It was the first development candidate selected from the quaternary ammonium carbapenems, which were eagerly studied since early 1980s. It contained a 1 β -methylcarbapenem skeleton and needed no coadministered drugs as meropenem, but its antibacterial profile, especially its antipseudomonal activity, resembled to that of imipenem.

Figure 20

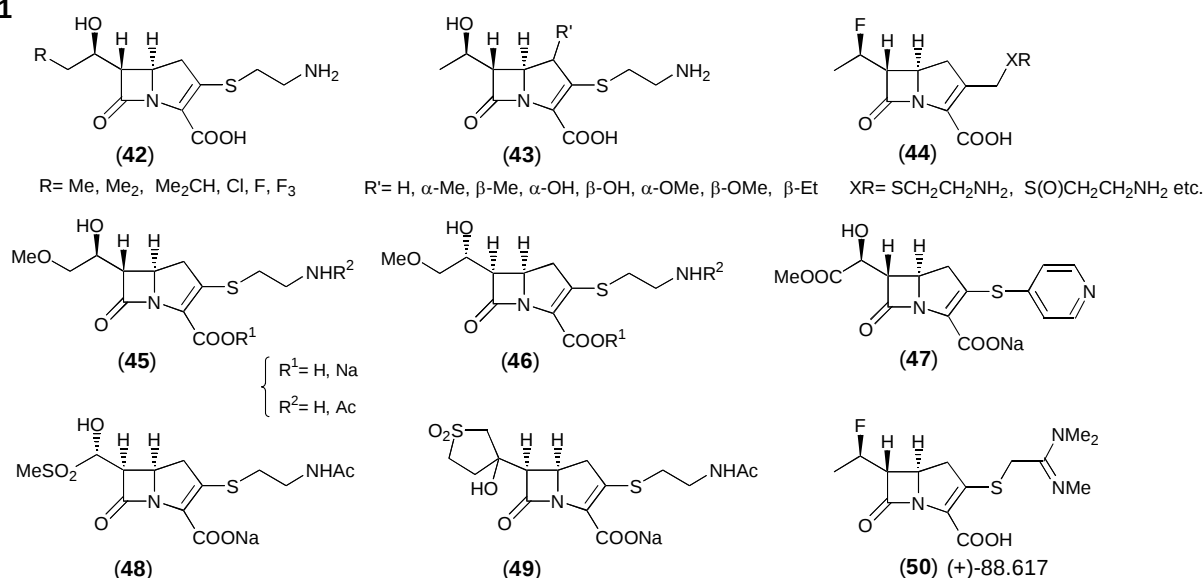


It should be noted that all three carbapenem antibiotics (2, 3 and 4), applied in the clinical use now, appeared together with biapenem (41), which was at the pre-registration stage, until the end of 1980s.

Moreover, the success of the 1 β -methyl introduction stimulated the investigation of modifying the substituents at other positions. The chemical modification at C6 was rather difficult and only natural types of chains had been synthesized until then. Studies were again conducted in the same vein. The following examples were found, but systematic studies were not reported because of the synthetic difficulties.

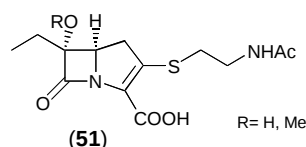
Firstly, modification of the ethyl group, that is, alkylation, oxygenation, and halogenation, decreased the antibacterial properties,^{2b,35-38} except for the fluorinated case (50).³⁹

Figure 21



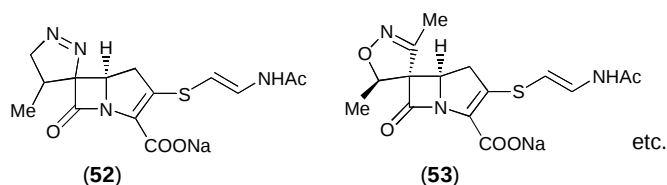
Secondly, the introduction of the methoxy group at C6, like a cephamycin antibiotic, significantly decreased the antibacterial activity.^{40,41}

Figure 22



The derivative having the spiro-type heterocycle at C6 was also synthesized.⁴²

Figure 23



Extension of the developmental studies on carbapenem antibiotics(1990-1999)

At the end of the 1980s, carbapenem synthetic chemistry was fundamentally established and it became rather easy to synthesize a wide range of carbapenem derivatives having a variety of substituents on the C1,C2 and C6 positions. As for the development of carbapenem antibiotics, a lot of valuable results in many SARs studies related to the antibacterial activity, physicochemical stability, metabolic stability and also side effects indicated several promising directions for development studies.

Therefore the developmental efforts in the 10 years of 1990s could be categorized into four directions as follows;

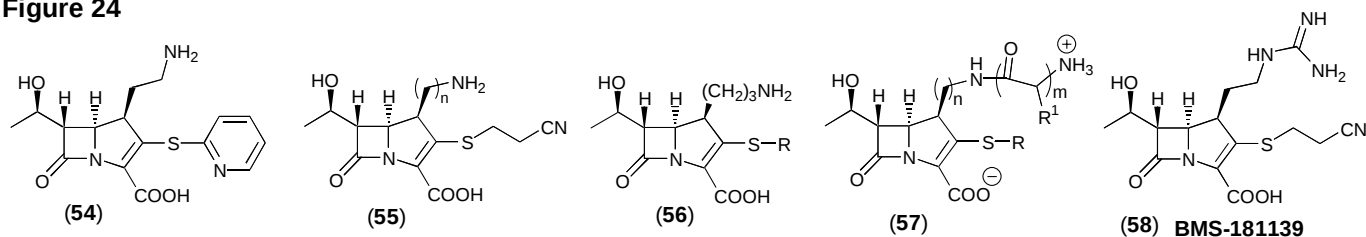
- 1, Design and introduction of new C1 substituents in carbapenems
- 2, Extension of the chemical modification of the C6 substituent in carbapenems
- 3, Evolution of new 1 β -methylcarbapenem antibiotics by the chemical modification of the C2 side-chain
- 4, Discovering novel approaches focused on carbapenem antibiotics having unique antibacterial profiles and/or chemical structures

In this chapter, these four directions of the development studies are mainly described.

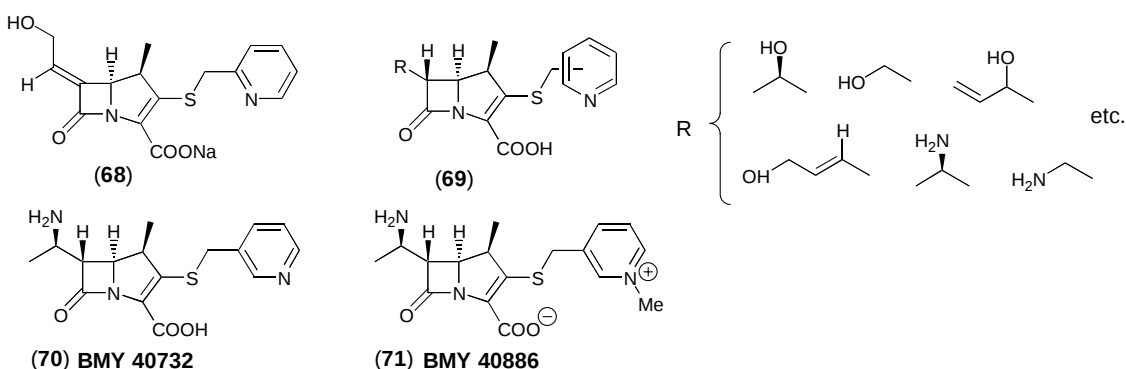
1) Introduction of a novel substituent at the C1 position

Since the first presentation at ICAAC in 1991, studies on a series of 1 β -aminoalkylcarbapenem derivatives were widely reported by the Bristol-Myers Squibb group.⁴³⁻⁴⁷

Figure 24

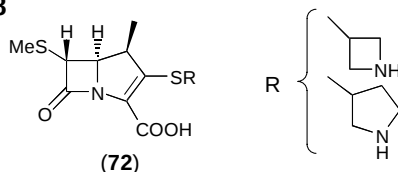


They also synthesized the compounds (60, 61) having an amino group at C6 and compared them with other derivatives (59), and (62~65) (Figure 25).⁴⁸ Through these extensive studies, they reported three notable findings. It was reconfirmed that the presence of a cationic center was essential to maintain or improve the antipseudomonal activity. The cationic moiety at C1 or C6 position was also effective for antipseudomonal activity, similar to that at the C2 position. The addition of a basic group at C1 or C6 position of a carbapenem already containing a cationic center at C2 position dissociated its necessity for porin protein D2 for activity which related to the overcoming of the resistance



Nagao *et al.* reported the synthesis of 6-methylthiocarbapenems (72) by utilizing the reactivity of α -anion in the β -lactam ring.⁵⁴

Figure 28



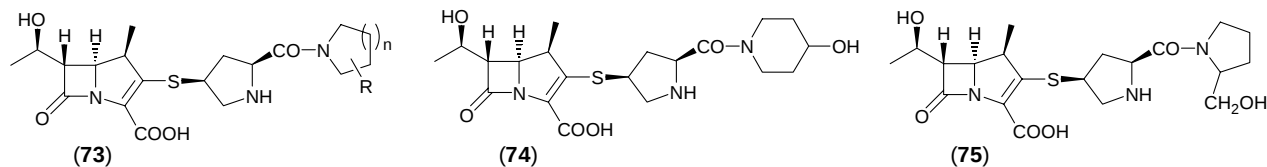
3) 1 β -Methylcarbapenems

As meropenem showed a good antibacterial profile including high antipseudomonal activity, the synthesis of a variety of derivatives having the 1 β -methylcarbapenem skeleton and 2,4-disubstituted pyrrolidine moiety at C2 was reported by many research groups.

Firstly, there were many derivatives which had amido group in the pyrrolidine ring, similar to meropenem.

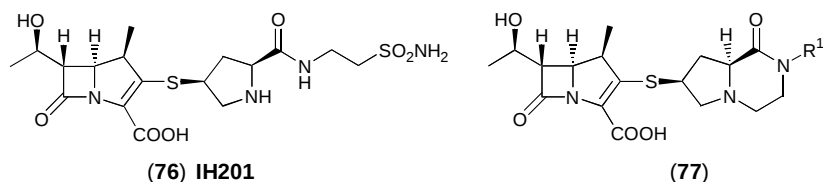
Oh *et al.* reported that the introduction of hydrophilic group on the amido moiety increased the antipseudomonal activity.⁵⁵

Figure 29



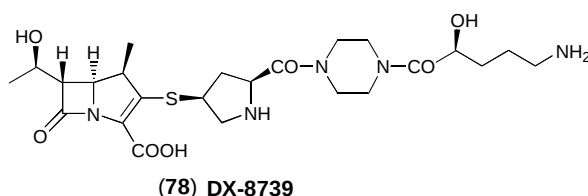
The following compounds showed antibacterial profile similar to meropenem.^{56,57}

Figure 30



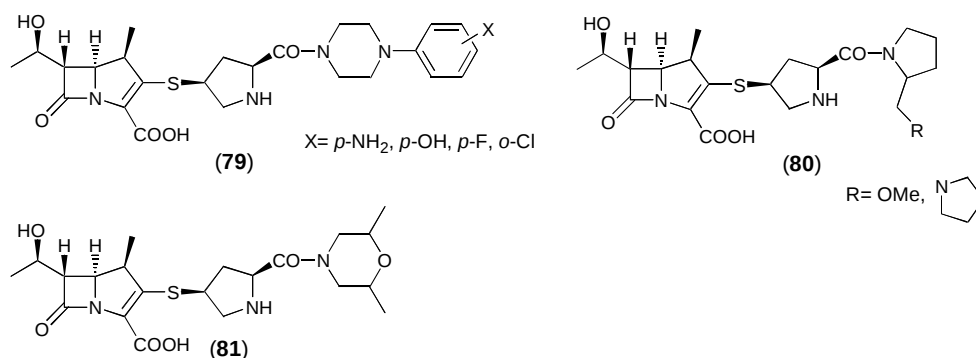
However, in most cases, an additional cationic (basic) center was added to improve the biological activities. Nishi *et al.* reported the piperazine derivative (78) which showed good antipseudomonal activity.⁵⁸

Figure 31



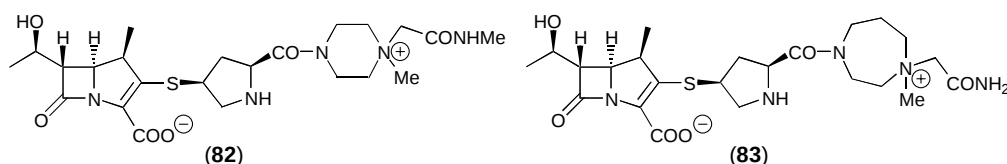
It is interesting that solely the following piperazine derivatives (**79**, *p*-NH₂, *p*-OH) showed good activity against *Pseudomonas aeruginosa*.⁵⁹

Figure 32



We reported the synthesis and the biological evaluation of a series of meropenem derivatives that had an extra quaternary ammonium moiety in the C2 proline side-chain. Compound **(82)** showed inhibition of tubular secretion and elongation of acting-time as a result.⁶⁰ A similar investigation was examined by the Sankyo group.⁶¹

Figure 33



It was interesting that Oh *et al.* reported the synthesis of the meropenem-type carbapenems having the sulfonium moiety as the extra cationic center.⁶²

Figure 34

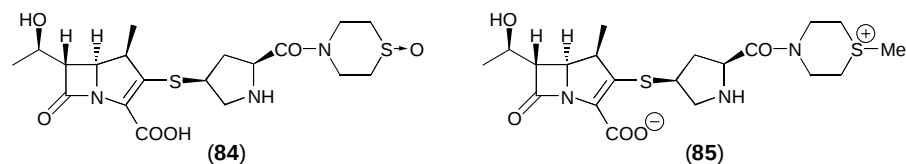
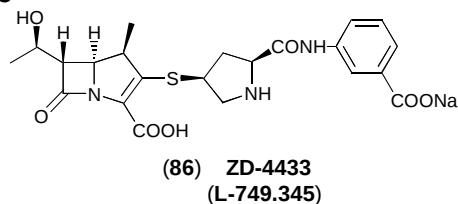


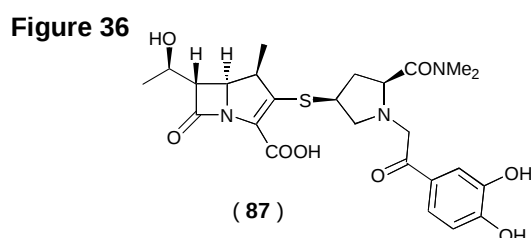
Figure 35



On the other hand, the Zeneca and Merck groups studied the introduction of an

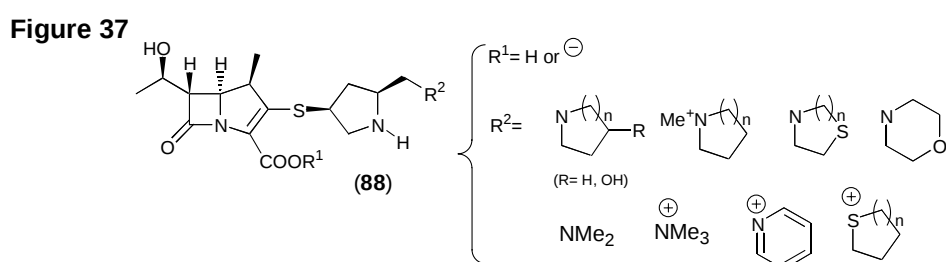
anionic moiety and found **ZD-4433 (86)** (Figure 35), which contained a carboxy group and showed a rather long acting-time in humans.⁶³ It is now under clinical evaluation.

We conducted another approach to introduce a catechol moiety as an additional functional group into meropenem. It was known in cephalosporin chemistry that the introduction of a catechol moiety markedly increased the activity against gram negative organisms, in particular *Pseudomonas aeruginosa* because this iron-chelating group allowed the β -lactam compound to behave as a siderophore mimic. It was confirmed that the *in vivo* antipseudomonal activity was improved by this modification.⁶⁴

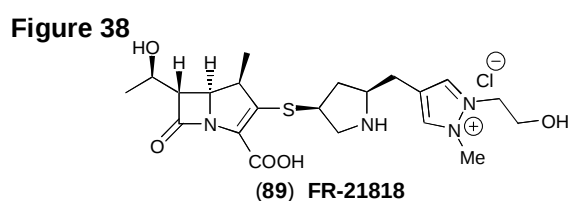


As an extension of the meropenem mimics, 2-substituted pyrrolidinylthio derivatives, of which the 2-substituents were substituted alkyl groups, were also synthesized. Several compounds in these derivatives showed excellent stability against DHP-I and exhibited potent antipseudomonal activity, as shown in the development process of meropenem in the last era.

Oh *et al.* reported that the introduction of a cationic group or a hydroxy group improved the antibacterial profile.⁶⁵



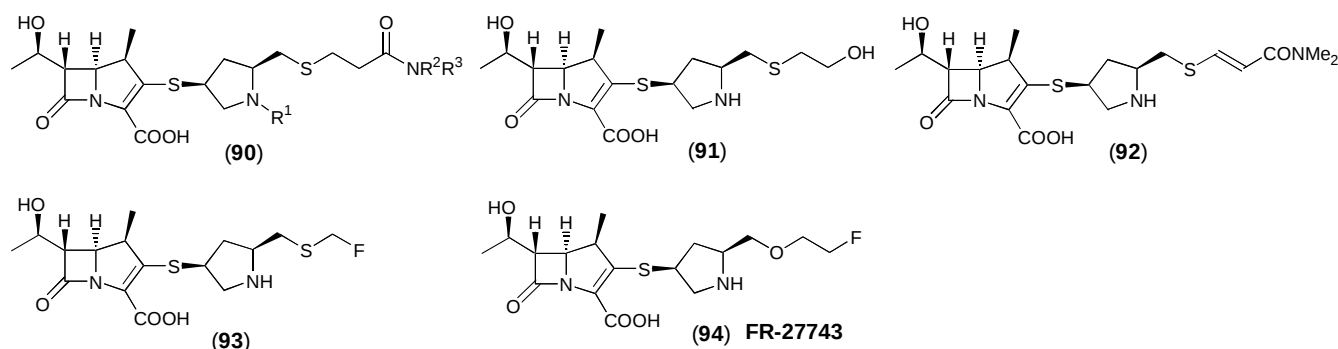
A further investigation on quaternization was examined by the Fujisawa group.⁶⁶



Lee *et al.* reported the synthesis of some sulfide derivatives⁶⁷ and the Fujisawa

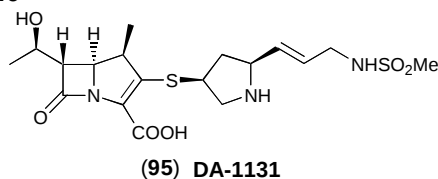
group also examined the insertion of a S or O atom in the C2 side-chain of the pyrrolidine ring.⁶⁸

Figure 39



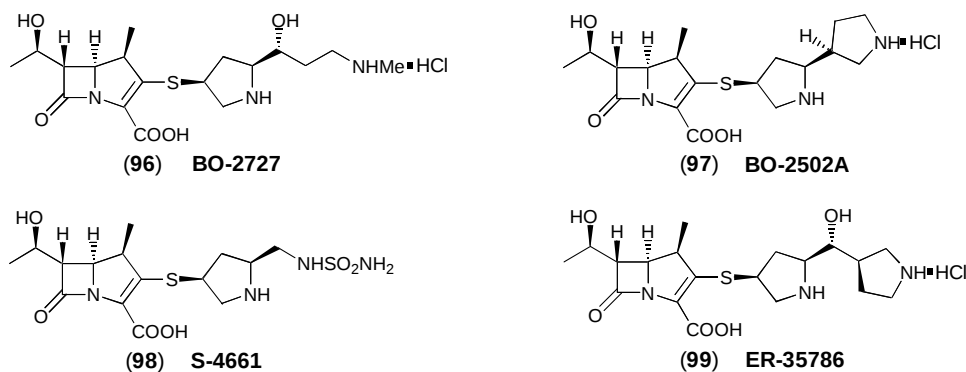
Elongation *via* the olefinic bond was reported by Kim *et al.*⁶⁹

Figure 40

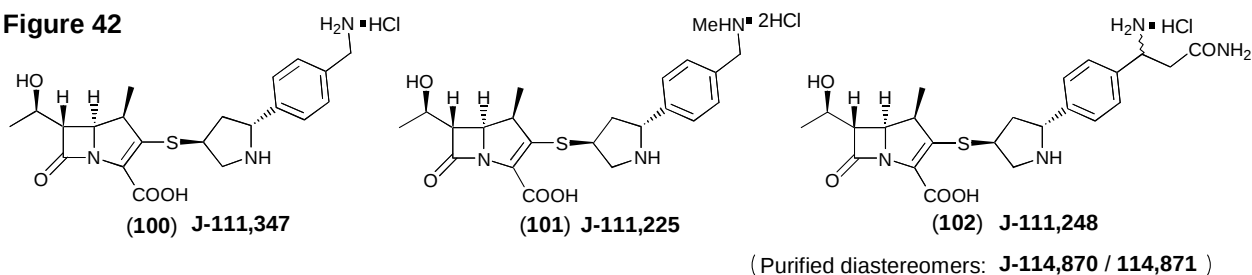


Although most compounds exhibited similar antimicrobial profile to that of meropenem, **BO-2727** (96) and related compounds by the Banyu group,⁷⁰ **S-4661** (98) by the Shionogi group,⁷¹ and **ER-35786** (99) by the Eisai group⁷² showed better anti-methicillin resistant *Staphylococcus aureus* (MRSA) activity. **S-4661** and **ER-35786** have now entered clinical trials.

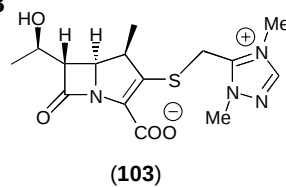
Figure 41



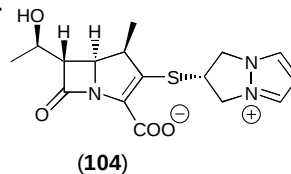
Recently the Banyu group reported the carbapenem compounds (100~102) that had potent antimicrobial activities against both of MRSA and *Pseudomonas aeruginosa* at ICAAC in 1998.⁷³

Figure 42

As for the quaternary ammonium-type carbapenems, exemplified by biapenem, further studies were not so extensively performed, and there were only a few reports. The Merck group reported that the monocyclic triazorium carbapenem (103) was nearly comparable in overall antibacterial activity and showed good stability against DHP-I to the four bicyclic heteroarylium analogs, as well as biapenem.⁷⁴

Figure 43

Recently, the Lederle group reported that the 1 β -methylcarbapenem bearing a σ -symmetric bicyclopiazoliumthio moiety showed good antibacterial activity.⁷⁵

Figure 44

4) Challenges in developing new types of carbapenem antibiotics

The progress of not only carbapenem chemistry but also detailed biological evaluations such as affinity for penicillin-binding proteins (PBPs), outer-membrane permeability, interaction with β -lactamases, mode of actions for multidrug efflux systems prompted many medicinal chemists to pursue the development of unique carbapenem antibiotics.

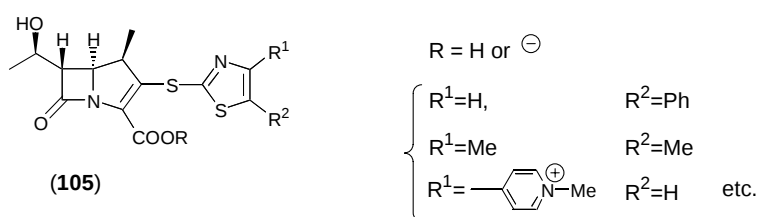
At the same time as the modifications of imipenem and meropenem etc. were proceeding, the studies on the development of new types of carbapenem antibiotics, having the different properties from imipenem or meropenem, from the aspects of antibacterial profile, pharmacokinetics, chemical structure/ property and so on, were performed. Studies on anti-MRSA carbapenems, hybrids of carbapenems and novel quinolones, orally active carbapenems, polycyclic carbapenems and some

other trials are described.

Anti-MRSA Carbapenem Antibiotics

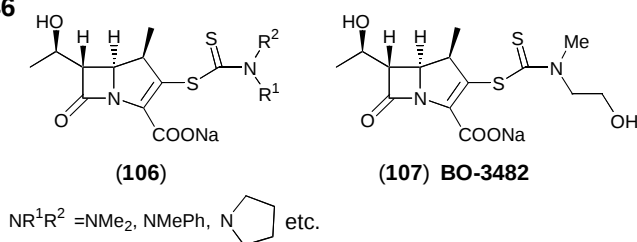
Among many bacterial pathogens, MRSA still remains as an important target for the development of anti-infective agents. It has been shown that these strains are also resistant to carbapenems. Although vancomycin has proven to be useful for treating staphylococcal infections, therapy with this drug is relatively limited because of its side effects. Therefore, potent anti-MRSA agents with a low level of side effects is highly desirable. One proposed resistance mechanism of MRSA to β -lactams is that penicillin binding protein-2' (PBP-2') produced in MRSA has a low affinity to β -lactams. We synthesized a series of novel 2-thiazolylthiocarbapenem derivatives which possessed excellent anti-MRSA activity together with high affinity to PBP-2'.⁷⁶ The Merck group reported similar results almost simultaneously.⁷⁷

Figure 45



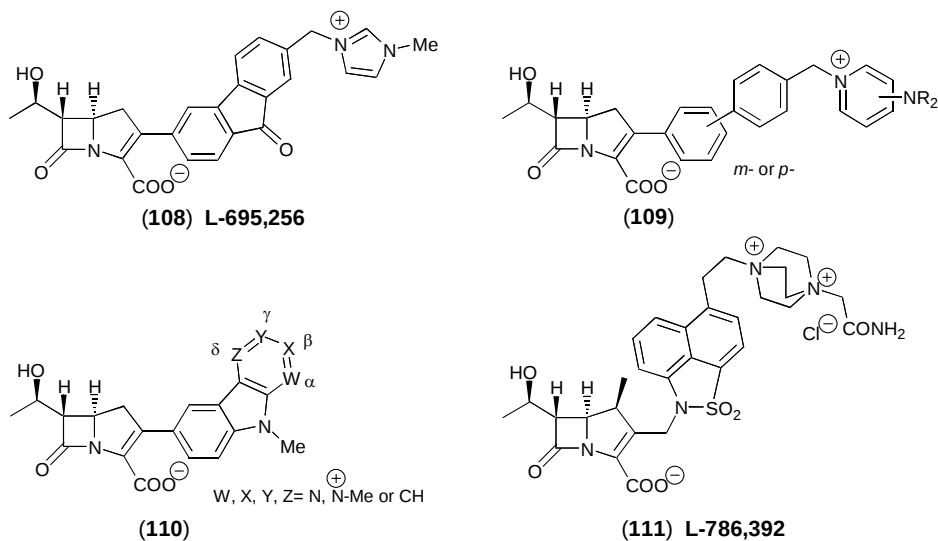
The dithiocarbamate carbapenems (106, 107) reported by the Banyu group could be classified in the above thiazole carbapenems, because the chemical structure of the dithiocarbamate group is closely related to that of the 2-thiazolylthio moiety.⁷⁸

Figure 46



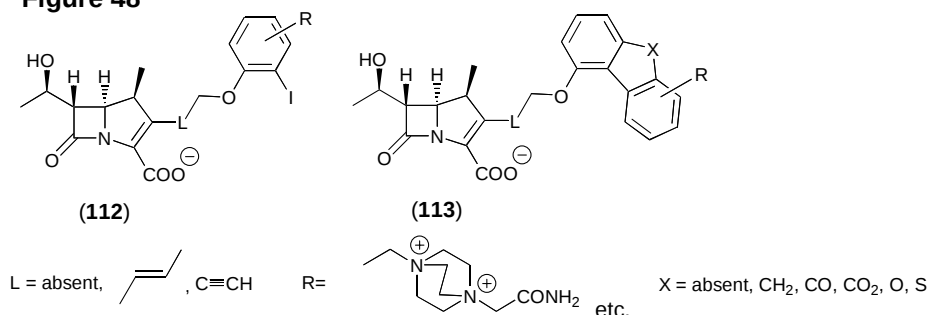
Several research groups have investigated the development of anti-MRSA carbapenems. To date, a variety of 2-arylcarbapenems were extensively investigated by the Merck group and the potent anti-MRSA and anti-methicillin resistant coagulase-negative staphylococci (MRCNS) activities of several compounds were reported.⁷⁹ Including L-786,392 (111) presented at ICAAC in 1998, most of the carbapenems possessed a quaternary nitrogen atom in the C2 aryl moiety. In these studies, it was suggested that the ammonium cation played an important role in the anti-MRSA activity.

Figure 47



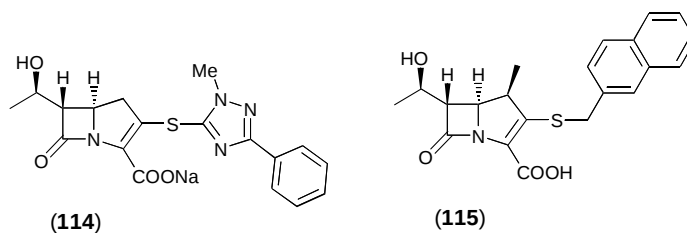
The Merck group reported another modification of the C2 side-chain for anti-MRSA carbapenems.⁸⁰

Figure 48



It was interesting that most of these carbapenems were derivatives in which the C2 side-chain was linked by a C-C bond instead of a C-S bond. There were a few reports relating to the C-S bonding derivatives such as 114 and 115 with the exception of 2-thiazolylthio-type carbapenems, described above.⁸¹

Figure 49

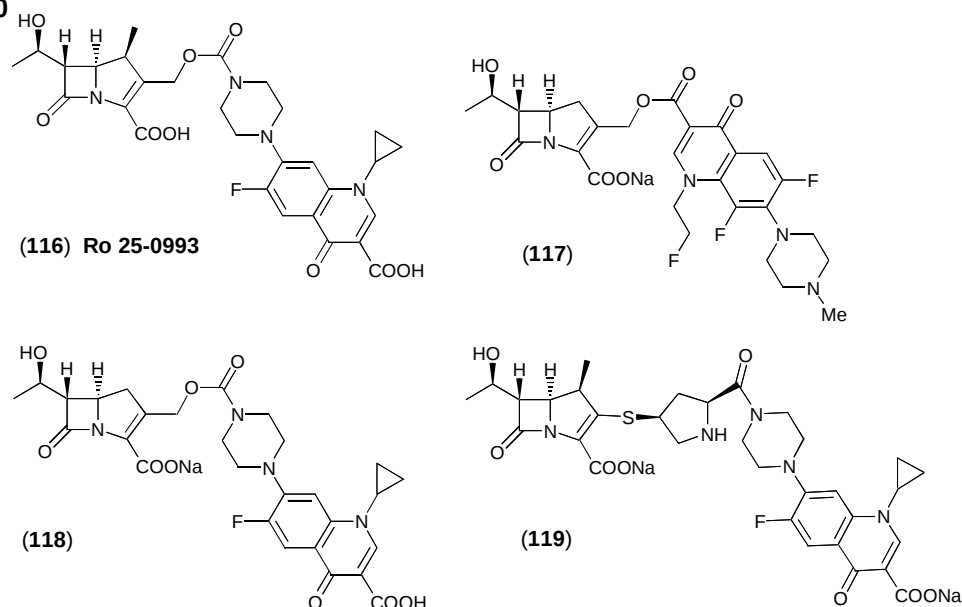


Recently, the studies on addition of anti-VRE (vancomycin-resistant enterococci) activity to the anti-MRSA carbapenems have been started.⁸²

Hybrids of Carbapenems and Novel Quinolones

The hybridized antibacterial properties of a carbapenem and a novel quinolone is quite attractive. A few trials were reported in order to achieve the synergetic effects of the excellent antibacterial properties of the hybrid.

Figure 50

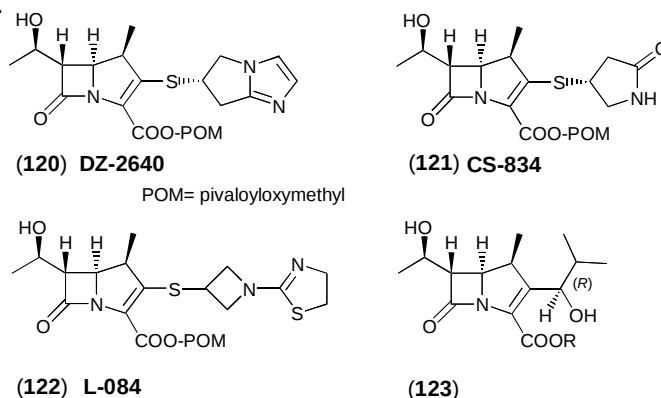


Firstly, the Roche group presented the synthesis and biological evaluation of **Ro 25-0993 (116)** at ICAAC in 1991⁸³ and they also reported **117** and **118** in the same series as **116**.⁸⁴ At ICAAC in 1996, the Procter & Gamble group also reported a hybrid of meropenem (**4**) and ciprofloxacin, both of which were representative compounds in their fields respectively.⁸⁵ However, the significant synergetic effects have not yet been reported from these studies.

Orally Active Carbapenem Antibiotics

As in the cases of the penicillin and cephalosporin antibiotics, of which both the injectable and the orally active ones were widely developed at the same time, the development of the orally active carbapenem antibiotics has also started to be studied. A few promising derivatives have already been reported.⁸⁶

Figure 51

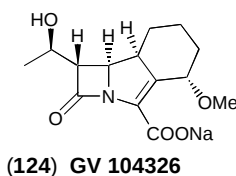


Most of these were prodrugs, of which the mother compounds showed well-balanced antibacterial activities except antipseudomonal activity. At present, CS-834 (121) and L-084 (122) are under clinical evaluation.

Polycyclic Carbapenem Antibiotics

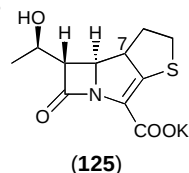
As a major modification of the carbapenem skeleton, multicyclic carbapenems have been synthesized. In particular, the Glaxo-Wellcome group thoroughly conducted SAR studies of tricyclic ones (trinems) and selected GV104326 (124) as a promising candidate.⁸⁷ Accompanied with the selection, much effort was concentrated on the development of stereoselective synthetic methodologies to this novel skeleton, and interesting synthetic routes were reported.

Figure 52



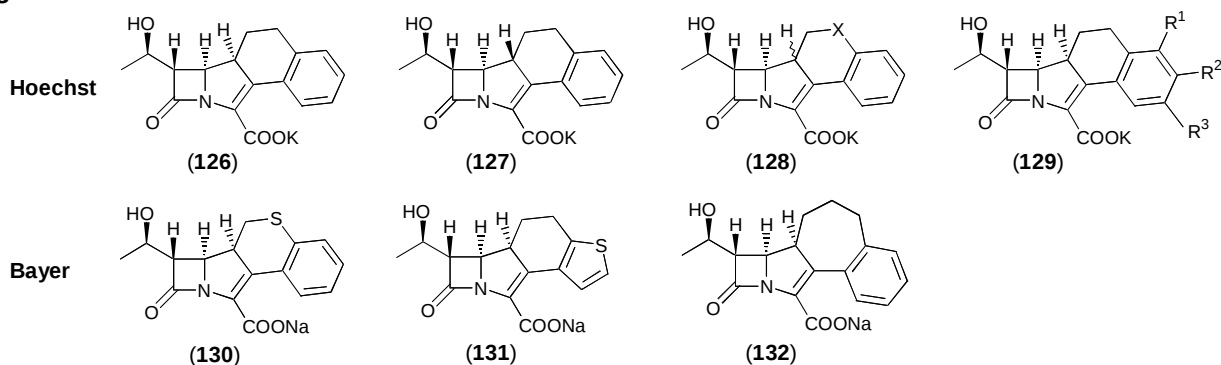
The synthesis and biological evaluation of the heterocyclic trinem (125) were also investigated. It was reported that 7 β isomer was difficult to purify due to its instability and more stable 7 α isomer showed weak antimicrobial activity.⁸⁸

Figure 53



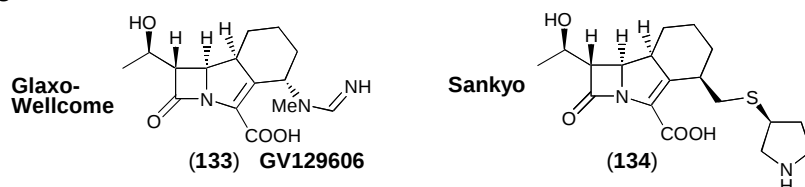
In the same period, tetracyclic derivatives were also synthesized, to evaluate their chemical and biological properties, by the Hoechst group.⁸⁹ Similar studies have been reported by the Bayer group.⁹⁰ But these studies were not fruitful from a viewpoint of the antibacterial activities.

Figure 54



Recently efforts to increase the antipseudomonal activity⁹¹ and anti-MRSA⁹² activity of the trinems were reported.

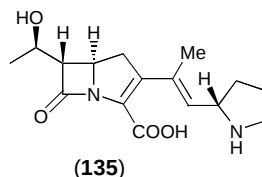
Figure 55



Miscellaneous trials

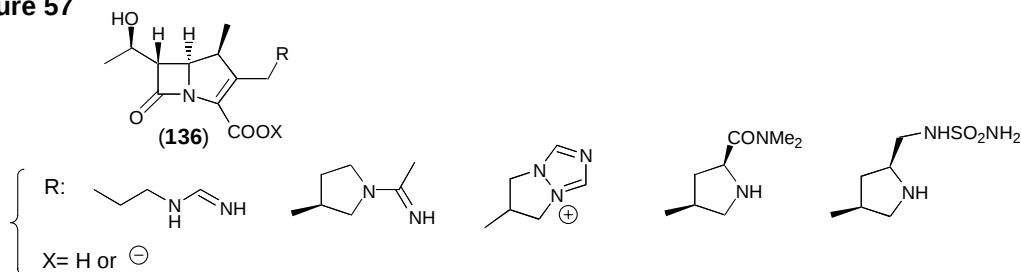
Effective modifications to improve significantly the stability against DHP-I, like the introduction of 1 β -methyl group, is still attractive in the carbapenem field. Yamada et al. reported that a type of 2-substituted vinyl carbapenems were very stable towards DHP-I.⁹³

Figure 56



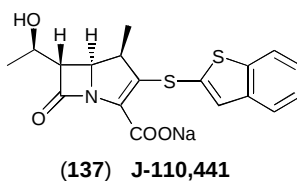
The Shionogi group synthesized dethiacarba analogs of imipenem, panipenem, biapenem, meropenem, and **S-4661** by utilizing palladium-catalyzed cross-coupling reaction of a carbapenem-2-yl triflate with an alkylborane. These 2-alkylcarbapenems (**Figure 57**), except for the biapenem analog, showed reduced activity compared with those of the parent thia derivatives.⁹⁴

Figure 57



Concerning the antimicrobial activity against certain gram negative bacteria, the presence of metallo- β -lactamases have been noted to relate to the emergence of carbapenem-resistant strains. Recently, the Banyu group reported that **J-110,441 (137) (Figure 58)**, having a benzothienylthio moiety at the C-2 position of 1 β -methylcarbapenem, was the most potent inhibitor of class B metallo- β -lactamases and combining imipenem or ceftazidime with it had a synergistic effect on the antimicrobial activity against β -lactamase-producing bacteria.⁹⁵

Figure 58



What will be expected in next generation carbapenem antibiotics ? (2000~)

The first generation carbapenem antibiotics such as imipenem and the new generation carbapenem antibiotic, meropenem, have been already applied widely in clinical use. Also some injectable carbapenems, such as biapenem, **S-4661**, **ZD-4433**, and **ER-35786** are under development. From a viewpoint of the antibacterial profile of these injectable carbapenems, they are similar with that of imipenem or meropenem. As imipenem and meropenem are sufficiently effective for treatment of the common bacterial infections, the unique carbapenems should clearly surpass these predecessors in activity against some carbapenem-insensitive pathogens, which cause serious infectious diseases. For example, antipseudomonal activity comparable with or greater than their potency against *Escherichia coli*, different mode of action in the antipseudomonal activity, which relates to the potent activity versus the carbapenem-resistant organisms, high anti-MRSA activity, and sufficient anti-VRE activity are expected. From a viewpoint of the structural aspects, chemical modifications of the substituents and the ring system on the 5-membered ring side have been performed and several useful findings reported. However, concerning the substituents on the β -lactam ring, especially at the C6 position, there seems to be enough possibilities to be explored concerning the next break-through, especially as modification of the corresponding sites in the fields of penicillin and cephalosporin antibiotics produced a variety of useful drugs. Even the most attractive C6-substituent at this moment, the 1-hydroxyethyl group, has no effects on improvement of the antibacterial activity itself, although it is effective in enhancing the stability against most β -lactamases. There are possibilities to find the next generation carbapenems by in depth investigations on the chemical modification of the C6 substituent. As for the development of the orally active carbapenem antibiotics (**CS-834**, **L-084** etc.), there are issues such as their necessity, criteria, and applying manner in the clinic to be discussed and clarified in order to avoid the emergence of carbapenem-resistant strains in the hospitals, based on the history of cephalosporin antibiotics development.

We hope that this article will be helpful in developing the next generation carbapenem antibiotics which are eagerly desired from the clinics of anti-infective therapy, especially from the big challenges that started in the period of 1990s.

REFERENCES

[†] Although most of the references in this article are cited from the published ones, some reports in "International Conference on Antimicrobial Agents and Chemotherapy (ICAAC)" are also adopted as the sources to explain clearly the researching history of carbapenem antibiotics from a viewpoint of their structural transition if they are helpful.

1. a) J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, D. Hendlin, S. Mochales, S. Hernandez, and H. B. Woodruff, Abstract 227, 16th Intersci. Conf. Antimicrob. Agents Chemother., Chicago, 1976. b) H. Kropp, J. S. Kahan, F. M. Kahan, J. Sandolf, G. Darland, and J. Birnbaum, Abstract 228, 16th Intersci. Conf. Antimicrob. Agents Chemother., Chicago, 1976. c) J. S. Kahan, F. M. Kahan, R. Gogelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff, and J. Birnbaum, *J. Antibiot.*, 1979, **32**, 1.
2. a) W. J. Leanza, K. J. Wildonger, J. Hannah, D. H. Shih, R. W. Ratcliffe, L. Barash, E. Walton, R. A. Firestone, G. F. Patel, F. M. Kahan, J. S. Kahan, and B. G. Christensen, Second International Symposium on "Recent Advances in the Chemistry of β -Lactam Antibiotics," ed. by G. I. Gregory, the Royal Society of Chemistry, 1980, p. 240. b) A. Andrus, F. Baker, F. A. Bouffard, L. D. Cama, B. G. Christensen, R. N. Guthikonda, J. V. Heck, D. B. R. Johnston, W. J. Leanza, R. W. Ratcliffe, T. N. Saltzmann, S. M. Schmitt, D. H. Shih, N. V. Shah, K. J. Wildonger, and R. R. Wilkening, Third International Symposium on "Recent Advances in the Chemistry of β -Lactam Antibiotics," ed. by A. G. Brown and S. M. Roberts, the Royal Society of Chemistry, 1984, p. 86. c) Y. Sugimura and T. Hiraoka, *Yakugaku Zasshi*, 1987, **107**, 175. d) Y. Fukagawa, N. Shibamoto, T. Yoshioka, and T. Ishikura, ' β -Lactam Antibiotics,' ed. by Y. Ueda and K. Shimizu, Nanko-do, 1987, p. 664. e) M. Sunagawa and A. Sasaki, *Yuki Gouseikagaku Kyokai Shi*, 1996, **54**, 761.
3. W. J. Leanza, K. J. Wildonger, T. W. Miller, and B. G. Christensen, *J. Med. Chem.*, 1979, **22**, 1435.
4. S. Sugawara, T. Miyadera, Y. Sugimura, S. Goto, and S. Kuwahara, Abstract 214, 22nd Intersci. Conf. Antimicrob. Agents Chemother., Chicago, 1982.
5. M. Sunagawa, H. Matsumura, T. Inoue, M. Fukasawa, and M. Kato, Abstract 752, 27th Intersci. Conf. Antimicrob. Agents Chemother., New York, 1987.
6. a) T. Kametani and M. Ihara, *Yuki Gouseikagaku Kyokai Shi*, 1980, **38**, 1025. b) T. Kametani, K. Fukumoto, and M. Ihara, *Heterocycles*, 1982, **17**, 463. c) R. W. Ratcliffe and G. Albers-Schönberg, 'Chemistry and Biology of β -Lactam Antibiotics,' Vol.2, ed. by R. B. Morin and M. Gorman, Academic Press, Inc.,

- New York, 1982, p. 227. d) M. Shibuya, *Yuki Gouseikagaku Kyokai Shi*, 1983, **41**, 62. e) W. Dürckheimer, J. Blumbach, R. Lattrell, and K. H. Scheunemann, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 180. f) T. Nagahara and T. Kametani, *Heterocycles*, 1987, **25**, 729. g) Y. Ito and S. Trerashima, *Yuki Gouseikagaku Kyokai Shi*, 1989, **47**, 606. h) C. Palomo, 'Recent Progress in the Chemical Synthesis of Antibiotics,' ed. by G. Lukacs and M. Ohno, Springer-Verlag, Berlin, 1990, p. 565. i) A. H. Berks, *Tetrahedron*, 1996, **52**, 331. j) A. Sasaki and M. Sunagawa, *Chem. Heterocycl. Compd. (N. Y.)*, 1999, **34**, 1249.
7. a) A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J. Chem. Soc., Chem. Comm.*, 1977, 523. b) K. Okamura, S. Hirata, Y. Okumura, Y. Fukagawa, Y. Shimauchi, K. Kouno, and T. Ishikura, *J. Antibiot.*, 1978, **31**, 480. c) M. Nakayama, A. Iwasaki, S. Kimura, T. Mizoguchi, S. Tanabe, A. Murakami, I. Watanabe, M. Okuchi, H. Itoh, Y. Saino, F. Kobayashi, and T. Mori, *J. Antibiot.*, 1980, **33**, 1388. d) K. Tanaka, J. Shoji, Y. Terui, N. Tsuji, E. Kondo, M. Miyama, Y. Kawamura, T. Hattori, K. Matsumoto, and T. Yoshida, *J. Antibiot.*, 1981, **34**, 909. e) N. Tsuji, K. Nagashima, M. Kobayashi, Y. Terui, K. Matsumoto, and E. Kondo, *J. Antibiot.*, 1982, **35**, 536.
8. a) D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 313. b) G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hershfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 6491. c) R. W. Ratcliffe, T. N. Salzmann, and B. G. Christensen, *Tetrahedron Lett.*, 1980, **21**, 31. d) D. G. Melillo, I. Shinkai, T. Liu, K. Ryan, and M. Sletzinger, *Tetrahedron Lett.*, 1980, **21**, 2783. e) I. Shinkai, *Yuki Gouseikagaku Kyokai Shi*, 2000, **58**, 432.
9. K. C. Nicolaou and E. J. Sorensen, 'Classics in Total Synthesis,' VCH Publishers, Inc., New York, 1996, p. 249.
10. D. W. Graham, W. T. Ashton, L. Barash, J. E. Brown, R. D. Brown, L. F. Canning, A. Chen, J. P. Springer, and E. F. Rogers, *J. Med. Chem.*, 1987, **30**, 1074.
11. L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 8006.
12. A. J. G. Baxter, P. Davis, R. J. Ponsford, and R. Southgate, *Tetrahedron Lett.*, 1980, **21**, 5071.
13. J. Hannah, C. R. Johnson, A. F. Wagner, and E. Walton, *J. Med. Chem.*, 1982, **25**, 457.
14. L. D. Cama, K. J. Wildonger, R. N. Guthikonda, R. W. Ratcliffe, and B. G. Christensen, *Tetrahedron*, 1983, **39**, 2531.
15. M. Shibuya and S. Kubota, *Tetrahedron Lett.*, 1981, **22**, 3611.
16. D. H. Shih, J. A. Fayter, F. Baker, L. Cama, and B. G. Christensen, Abstract

- 333, 23rd Intersci. Conf. Antimicrob. Agents Chemother., Las Vegas, 1983.
17. D. H. Shih, F. Baker, L. Cama, and B. G. Christensen, *Heterocycles*, 1984, **21**, 29.
18. D. H. Shih, L. Cama, and B. G. Christensen, *Tetrahedron Lett.*, 1985, **26**, 587.
19. T. Shibata and Y. Sugimura, *J. Antibiot.*, 1989, **42**, 374.
20. C. U. Kim, B. Y. Luh, P. F. Misco, and M. J. M. Hitchcock, *J. Med. Chem.*, 1989, **32**, 601.
21. R. N. Guthikonda, L. D. Cama, M. Quesada, M. F. Woods, T. N. Salzmann, and B. G. Christensen, *J. Med. Chem.*, 1987, **30**, 871.
22. S. M. Schmitt, T. N. Salzmann, D. H. Shih, and B. G. Christensen, *J. Antibiot.*, 1988, **41**, 780.
23. T. N. Salzmann, F. P. DiNinno, M. L. Greenlee, R. N. Guthikonda, M. L. Quesada, S. M. Schmitt, J. J. Herrmann, and M. F. Woods, Fourth International Symposium on "Recent Advances in the Chemistry of β -Lactam Antibiotics," ed. by P. H. Bentley and R. Southgate, the Royal Society of Chemistry, 1989, p.171.
24. J. Haruta, K. Nishi, K. Kikuchi, S. Matsuda, Y. Tamura, and Y. Kita, *Chem. Pharm. Bull.*, 1989, **37**, 2338.
25. T. Shibata, K. Iino, T. Tanaka, T. Hashimoto, Y. Kameyama, and Y. Sugimura, *Tetrahedron Lett.*, 1985, **26**, 4739.
26. E. Goetschi, P. Angehrn, and R. Then, Abstract 759, 27th Intersci. Conf. Antimicrob. Agents Chemother., New York, 1987.
27. Y. Nagao, T. Abe, H. Shimizu, T. Kumagai, and Y. Inoue, *J. Chem. Soc., Chem. Commun.*, 1989, 821.
28. R. L. Rosati, L. V. Kapili, P. Morrissey, and J. A. Retsema, *J. Med. Chem.*, 1990, **33**, 291.
29. N. V. Shah and L. D. Cama, *Heterocycles*, 1987, **25**, 221.
30. M. Sunagawa, H. Matsumura, T. Inoue, M. Fukasawa, and M. Kato, *J. Antibiot.*, 1990, **43**, 519.
31. M. Sunagawa, H. Matsumura, T. Inoue, M. Fukasawa, and M. Kato, *J. Antibiot.*, 1991, **44**, 459.
32. M. Sunagawa, H. Matsumura, T. Inoue, H. Yamaga, and M. Fukasawa, *J. Antibiot.*, 1992, **45**, 971.
33. M. Sunagawa, H. Matsumura, and M. Fukasawa, *J. Antibiot.*, 1992, **45**, 1983.
34. a) M. Hikida, M. Yoshida, K. Nishiki, Y. Furukawa, K. Ubukata, M. Konno, and S. Mitsunashi, Abstract 221, 29th Intersci. Conf. Antimicrob. Agents Chemother., Houston, 1989. b) Y. Nagao, Y. Nagase, T. Kumagai, H. Matsunaga, T. Abe, O. Shimada, T. Hayashi, and Y. Inoue, *J. Org. Chem.*, 1992, **57**, 4243.
35. J. G. de Vries, G. Sigmund, and G. Vorisek, *Heterocycles*, 1985, **23**, 1915.

36. M. Ohtani, F. Watanabe, and M. Narisada, *J. Antibiot.*, 1985, **38**, 610.
37. D. Häbich and W. Hartwig, *Tetrahedron Lett.*, 1987, **28**, 781.
38. N. Tamura, H. Natsugari, Y. Kawano, Y. Matsushita, K. Yoshioka, and M. Ochiai, *Chem. Pharm. Bull.*, 1987, **35**, 996.
39. T. Yoshioka, A. Watanabe, N. Chida, and Y. Fukagawa, *J. Antibiot.*, 1989, **42**, 1520.
40. T. Yoshioka, A. Watanabe, K. Isshiki, Y. Fukagawa, and T. Ishikura, *Tetrahedron Lett.*, 1986, **27**, 4335.
41. A. Watanabe, Y. Fukagawa, T. Ishikura, and T. Yoshioka, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 2091.
42. D. F. Corbett, *J. Chem. Soc., Perkin Trans. I*, 1986, 421.
43. A. Martel, J. Banville, C. Bachand, G. Bouthillier, J. Corbeil, J. Fung-Tomc, P. Lapointe, H. Mastalerz, V. S. Rao, R. Remillard, B. Turmel, M. Menard, R. E. Kessler, and R. A. Partyka, Abstract 827, 31st Intersci. Conf. Antimicrob. Agents Chemother., Chicago, 1991.
44. J. Banville, C. Bachand, J. Corbeil, J. Desiderio, J. Fung-Tomc, P. Lapointe, A. Martel, V. S. Rao, R. Remillard, M. Menard, R. E. Kessler, and R. A. Partyka, Abstract 828, 31st Intersci. Conf. Antimicrob. Agents Chemother., Chicago, 1991.
45. C. Bachand, J. Banville, G. Bouthillier, J. Corbeil, J. P. Daris, J. Desiderio, J. Fung-Tomc, P. Lapointe, A. Martel, H. Mastalerz, R. Remillard, Y. Tsai, M. Menard, R. E. Kessler, and R. A. Partyka, Abstract 829, 31st Intersci. Conf. Antimicrob. Agents Chemother., Chicago, 1991.
46. V. S. Rao, C. Bachand, J. Banville, G. Bouthillier, J. Desiderio, J. Fung-Tomc, P. Lapointe, A. Martel, H. Mastalerz, R. Remillard, A. Michel, M. Menard, R. E. Kessler, and R. A. Partyka, Abstract 830, 31st Intersci. Conf. Antimicrob. Agents Chemother., Chicago, 1991.
47. R. E. Kessler, J. Fung-Tomc, B. Minassian, B. Kolek, E. Huczko, and D. P. Bonner, Abstract F42, 34th Intersci. Conf. Antimicrob. Agents Chemother., Orlando, 1994.
48. J. Fung-Tomc, E. Huczko, J. Banville, M. Ménard, B. Kolek, E. Gradelski, B. Minassian, R. E. Kessler, and D. P. Bonner, *Antimicrob. Agents Chemother.*, 1995, **39**, 394.
49. E. H. Ruediger and C. Solomon, *J. Org. Chem.*, 1991, **56**, 3183.
50. H. Mastalerz and M. Ménard, *Heterocycles*, 1991, **32**, 93.
51. G. Bouthillier, H. Mastalerz, M. Ménard, J. Fung-Tomc, and E. Gradelski, *J. Antibiot.*, 1992, **45**, 240.
52. H. Mastalerz, M. Ménard, E. Ruediger, and J. Fung-Tomc, *J. Med. Chem.*, 1992, **35**, 953.
53. V. S. Rao, R. Rémillard, and M. Ménard, *Heteroat. Chem.*, 1992, **3**, 25.

54. Y. Nagao, T. Abe, H. Shimizu, T. Kumagai, and Y. Inoue, *Heterocycles*, 1992, **33**, 523.
55. C. H. Oh, S. Y. Hong, and J. H. Cho, *Korean J. Med. Chem.*, 1992, **2**, 7.
56. K. J. Shin, K. H. Yoo, D. J. Kim, S. W. Park, B. S. Ko, S. J. Lee, J. D. Hue, and S. Y. Park, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1607.
57. M.-H. Kim, K.-J. Shin, and S.-W. Park, *Korean J. Med. Chem.*, 1994, **4**, 16.
58. T. Nishi, M. Takemura, T. Saito, Y. Ishida, K. Sugita, M. Houmura, H. Ishii, K. Sato, I. Hayakawa, and T. Hayano, Abstract 131, 32nd Intersci. Conf. Antimicrob. Agents Chemother., Anaheim, 1992.
59. H.-W. Lee, E.-N. Kim, K.-K. Kim, H.-J. Son, J.-K. Kim, C.-R. Lee, and J.-W. Kim, *Korean J. Med. Chem.*, 1994, **4**, 101.
60. M. Sunagawa, A. Sasaki, H. Yamaga, H. Shinagawa, Y. Sumita, and H. Nouda, *J. Antibiot.*, 1994, **47**, 1337.
61. K. Ishikawa, K. Kojima, M. Miyauchi, R. Endo, H. Yasuda, and I. Kawamoto, *J. Antibiot.*, 1998, **51**, 757.
62. C.-H. Oh and J.-H. Cho, *J. Antibiot.*, 1994, **47**, 126.
63. B. A. Pelak, L. S. Gerckens, K. Dorso, C. Pacholok, L. Lynch, J. Kahan, D. Shungu, and H. Kropp, Abstract F119, 36th Intersci. Conf. Antimicrob. Agents Chemother., New Orleans, 1996.
64. M. Sunagawa, A. Sasaki, H. Yamaga, H. Shinagawa, M. Fukasawa, and Y. Sumita, *J. Antibiot.*, 1994, **47**, 1354.
65. C. H. Oh, E. R. Woo, S. Seo, S. Y. Hong, K. Nam, D. Kim, and J. H. Cho, *Korean J. Med. Chem.*, 1994, **4**, 26.
66. Y. Matsumoto, S. Matsumoto, C. Morinaga, S. Tawara, A. Tanaka, D. Barrett, K. Matsuda, T. Chiba, and K. Sakane, Abstract F146, 35th Intersci. Conf. Antimicrob. Agents Chemother., San Francisco, 1995.
67. a) H.-W. Lee, E.-N. Kim, H.-J. Son, K.-K. Kim, J.-K. Kim, C.-R. Lee, and J.-W. Kim, *J. Antibiot.*, 1995, **48**, 1046. b) H.-W. Lee, E.-N. Kim, H.-J. Son, Soon-Kil Ahn, K.-H. Chung, J.-W. Kim, and C.-R. Lee, *Chem. Pharm. Bull.*, 1996, **44**, 2326. c) H.-W. Lee, E.-N. Kim, T. W. Kang, S.-K. Ahn, N.-H. Choi, J.-W. Kim, and C. I. Hong, *J. Antibiot.*, 1997, **50**, 1078.
68. a) H. Azami, H. Tsutsumi, K. Matsuda, D. Barrett, K. Hattori, T. Nakajima, S. Kuroda, T. Kamimura, and M. Murata, *Bioorg. Med. Chem.*, 1997, **5**, 2069. b) H. Azami, K. Matsuda, H. Tsutsumi, T. Kamimura, and M. Murata, *J. Antibiot.*, 1998, **51**, 374.
69. H. Kim, H. J. Shim, W. B. Kim, and M. G. Lee, *Antimicrob. Agents Chemother.*, 1998, **42**, 1217.
70. a) O. Okamoto, H. Fukatsu, S. Nakagawa, and N. Tanaka, Abstract 898, 33rd Intersci. Conf. Antimicrob. Agents Chemother., New Orleans, 1993. b) N. Ohtake, E. Mano, R. Ushijima, M. Sanada, S. Nakagawa, and N. Tanaka, Abstract 921, 33rd Intersci. Conf. Antimicrob. Agents Chemother., New Orleans, 1993. c) N. Ohtake, O. Okamoto, S. Kato, R. Ushijima, Y. Kato, H.

- Fukatsu, and S. Nakagawa, *J. Antibiot.*, 1997, **50**, 586. d) N. Ohtake, K. Yamada, E. Mano, O. Okamoto, R. Ushijima, and S. Nakagawa, *J. Antibiot.*, 1997, **50**, 567.
71. a) S. Sasaki, K. Murakami, Y. Nishitani, and S. Kuwahara, Abstract F33, 34th Intersci. Conf. Antimicrob. Agents Chemother., Orlando, 1994. b) Y. Iso, T. Irie, Y. Nishino, K. Motokawa, and Y. Nishitani, *J. Antibiot.*, 1996, **49**, 199.
72. N. Sato, M. Sasho, A. Kamada, T. Suzuki, K. Ashizawa, and I. Sugiyama, Abstract F151, 35th Intersci. Conf. Antimicrob. Agents Chemother., San Francisco, 1995.
73. a) A. Shimizu, H. Sugimoto, S. Sakuraba, H. Imamura, H. Sato, N. Ohtake, R. Ushijima, S. Nakagawa, C. Suzuki, T. Hashizume, and H. Morishima, Abstract F-52, 38th Intersci. Conf. Antimicrob. Agents Chemother., San Diego, 1998. b) Y. Adachi, R. Nagano, K. Shibata, Y. Kato, T. Hashizume, and H. Morishima, Abstract F-54, 38th Intersci. Conf. Antimicrob. Agents Chemother., San Diego, 1998. c) R. Nagano, Y. Adachi, T. Hashizume, and H. Morishima, Abstract F-55, 38th Intersci. Conf. Antimicrob. Agents Chemother., San Diego, 1998.
74. K. J. Wildonger and R. W. Ratcliffe, *J. Antibiot.*, 1993, **46**, 1866.
75. Y. Nagao, S. Tamai, N. Tanigawa, S. Sano, T. Kumagai, and I. Kishi, *Heterocycles*, 1998, **48**, 617.
76. a) M. Sunagawa, H. Yamaga, H. Shinagawa, H. Houchigai, and Y. Sumita, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 2793. b) H. Shinagawa, H. Yamaga, H. Houchigai, Y. Sumita, and M. Sunagawa, *Bioorg. Med. Chem.*, 1997, **5**, 601.
77. S. T. Waddell, R. W. Ratcliffe, S. P. Szumiloski, K. J. Wildonger, R.R. Wilkening, T. A. Blizzard, J. Huber, J. Kohler, K. Dorso, E. St. Rose, J. G. Sundelof, and G. G. Hammond, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1427.
78. a) N. Ohtake, H. Kiyonaga, M. Ogawa, H. Imamura, S. Okada, H. Jona, A. Shimizu, M. Moriya, H. Sato, Y. Tominaga, K. Yamada, H. Kondo, K. Torigoe, M. Nakano, R. Ushijima, and S. Nakagawa, Abstract F-117, 36th Intersci. Conf. Antimicrob. Agents Chemother., New Orleans, 1996. b) N. Ohtake, H. Imamura, H. Jona, H. Kiyonaga, A. Shimizu, M. Moriya, H. Sato, M. Nakano, R. Ushijima, and S. Nakagawa, *Bioorg. Med. Chem.*, 1998, **6**, 1089.
79. a) M. Sasor, L. Cama, M. L. Greenlee, F. P. DiNinno, and J. V. Heck, Abstract F50, 34th Intersci. Conf. Antimicrob. Agents Chemother., Orlando, 1994. b) F. DiNinno, D. A. Muthrad, T. N. Salzmann, J. Huber, J. Kahan, and H. Kropp, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 945. c) L. C. Meurer, R. N. Guthikonda, J. L. Huber, and F. DiNinno, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 767. d) K. D. Dykstra and F. Dininno, *Tetrahedron Lett.*, 1998, **39**, 1865. e) K. L. Dorso, J. Kohler, H. Kropp, H. Rosen, and L. L. Silver, Abstract F-28, 38th Intersci. Conf. Antimicrob. Agents Chemother., San Diego, 1998.
80. F. DiNinno, H. Y. Chen, K. D. Dykstra, and M. L. Hammond, Abstract F-34, 38th Intersci. Conf. Antimicrob. Agents Chemother., San Diego, 1998.

81. a) C. Fiakpui, G. Thomas, M. P. Singh, R. G. Micetich, and R. Singh, *J. Antibiot.*, 1996, **49**, 212. b) J. C. Arnould, R. N. Illingworth, W. W. Nichols, and R. G. Willson, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2449.
82. T. Toyosawa and M. Inoue, Abstract 380, 39th Intersci. Conf. Antimicrob. Agents Chemother., San Francisco, 1999.
83. A. J. Corraz, S. L. Dax, N. K. Dunlap, D. D. Keith, D. L. Pruess, P. L. Rossman, J. Unowsky, and C. -C. Wei, Abstract 826, 31st Intersci. Conf. Antimicrob. Agents Chemother., Chicago, 1991.
84. A. J. Corraz, S. L. Dax, N. K. Dunlap, N. H. Georgopapadakou, D. D. Keith, D. L. Pruess, P. L. Rossman, R. Then, J. Unowsky, and C. -C. Wei, *J. Med. Chem.*, 1992, **35**, 1828.
85. P. M. Hershberger, A. G. Switzer, K. E. Yelm, M. C. Coleman, C. A. Devries, F. J. Rourke, B. W. Davis, W. G. Kraft, T. L. Twinem, P. M. Koenigs, S. M. Paule, R. J. Siehnel, P. H. Zoutendam, R. Imbus, and T. P. Demuth, Jr., Abstract F170, 36th Intersci. Conf. Antimicrob. Agents Chemother., New Orleans, 1996.
86. a) T. Nishi, Y. Ishida, K. Sugita, M. Ohtsuka, M. Takemura, I. Hayakawa, and T. Hayano, Abstract F133, 35th Intersci. Conf. Antimicrob. Agents Chemother., San Francisco, 1995. b) I. Kawamoto, M. Miyauchi, R. Endo, M. Hisaoka, H. Yasuda, and S. Kuwahara, Abstract F105, 36th Intersci. Conf. Antimicrob. Agents Chemother., New Orleans, 1996. c) T. Abe, K. Hayashi, A. Mihira, C. Satoh, S. Tamai, S. Yamamoto, M. Hikida, T. Kumagai, and M. Kitamura, Abstract F-64, 38th Intersci. Conf. Antimicrob. Agents Chemother., San Diego, 1998. d) J. H. Kim, J. S. Lee, D. K. Pyun, and C. H. Lee, Abstract F-46, 38th Intersci. Conf. Antimicrob. Agents Chemother., San Diego, 1998.
87. a) A. Perboni, D. Donati, T. Rossi, B. Tamburini, G. Tarzia, and G. Gaviraghi, Abstract 127, 32nd Intersci. Conf. Antimicrob. Agents Chemother., Anaheim, 1992. b) A. Perboni, B. Tamburini, T. Rossi, D. Donati, G. Tarzia, and G. Gaviraghi, *Spec. Publ. - R. Soc. Chem. (Recent Advances in the Chemistry of Anti-Infective Agents)*, 1993, **119**, 21. c) S. Hanessian, M. J. Rozema, G. B. Reddy, and J. F. Braganza, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 2535. d) D. Andreotti, T. Rossi, G. Gaviraghi, D. Donati, C. Marchioro, E. D. Modugno, and A. Perboni, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 491. e) M. E. Tranquillini, G. L. Araldi, D. Donati, G. Pentassuglia, A. Pezzoli, and A. Ursini, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1683. f) S. Biondi, G. Gaviraghi, and T. Rossi, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 525. g) S. Biondi, E. Piga, T. Rossi, and G. Vigelli, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2061. h) S. Hanessian and M. J. Rozema, *J. Am. Chem. Soc.*, 1997, **118**, 9884. i) S. Hanessian, A.M. Griffin, and M. J. Rozema, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1857.
88. R. D. Fabio, A. Feriani, G. Gaviraghi, and T. Rossi, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1235.
89. T. Wollmann, U. Gerlach, R. Hörlein, N. Krass, R. Lattrell, M. Limbert, and A.

- Markus, *Spec. Publ. - R. Soc. Chem. (Recent Advances in the Chemistry of Anti-Infective Agents)*, 1993, **119**, 50.
90. G. Schmidt, W. Schröck, and R. Endermann, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 2193.
91. E. D. Modugno, R. Broggio, I. Erbeti, and J. Lowther, *Antimicrob. Agents Chemother.*, 1997, **41**, 2742.
92. O. Kanno, Y. Shimoji, S. Ohya, and I. Kawamoto, *J. Antibiot.*, 2000, **53**, 404.
93. A. Yamada, K. Hattori, S. Kuroda, T. Chiba, T. Kamimura, and K. Sakane, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2705.
94. Y. Narukawa, K. Nishi, and H. Onoue, *Tetrahedron*, 1997, **53**, 539.
95. a) R. Nagano, K. Yamada, Y. Sugimoto, H. Imamura, T. Hashizume, and H. Morishima, Abstract 402, 39th Intersci. Conf. Antimicrob. Agents Chemother., San Francisco, 1999. b) R. Nagano, Y. Adachi, H. Imamura, K. Yamada, T. Hashizume, and H. Morishima, *Antimicrob. Agents Chemother.*, 1999, **43**, 2497.