Current Status of Oral Carbapenem Development

Toshio Kumagai*, Satoshi Tamai, Takao Abe and Muneo Hikida

Medical Research Laboratories, Wyeth Lederle (Japan) Ltd., 1-6-34, Kashiwa-cho, Shiki-shi, Saitama 353-8511, Japan

Abstract: Since the discovery of thienamycin (**1**) in 1976, many studies on the synthesis and structure-activity relationships of parenteral-use drugs have been done and several carbapenems, imipenem (**2**), panipenem (**3**), and meropenem (**7**), have been marketed.

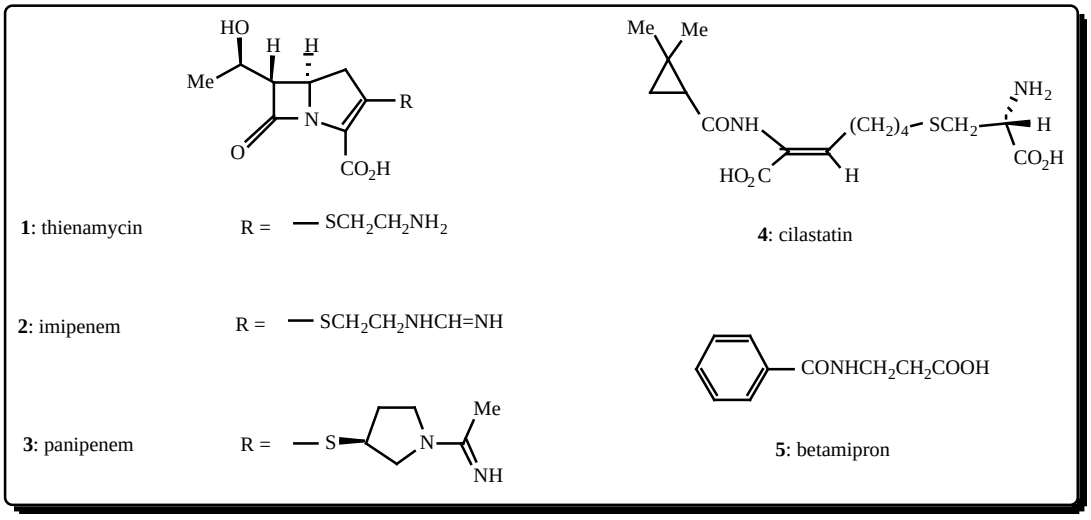
The development of oral carbapenems, however, is a fairly slow process because carbapenems are considered unstable in the stomach and intestine. Recently, several orally active carbapenems without stability problems have been developed as prodrug esters or prodrug peptides, including GV-118819 (**12**), CS-834 (**13**), L-084 (**14**), DZ-2640 (**15**), and peptidic derivatives of CL 191,121 (**16**). The active forms (**35**), (**41**), (**44**), (**45**), (**16**) of these prodrugs exhibited potent and well balanced antibacterial activities as well as resistance to renal dehydropeptidase-I. The pharmacokinetic parameters of compounds (**12**), (**13**), (**14**), and (**15**) after oral administration to healthy volunteers were reported. The half-life ($t_{1/2}$) of GV-118819 (**12**) was longer than that of the other compounds, while the Cmax, AUC and urinary excretion rate of L-084 (**14**) were higher than those of the others.

In this review, the synthesis, chemical and biological properties, and pharmacokinetics of these oral carbapenems are described.

INTRODUCTION

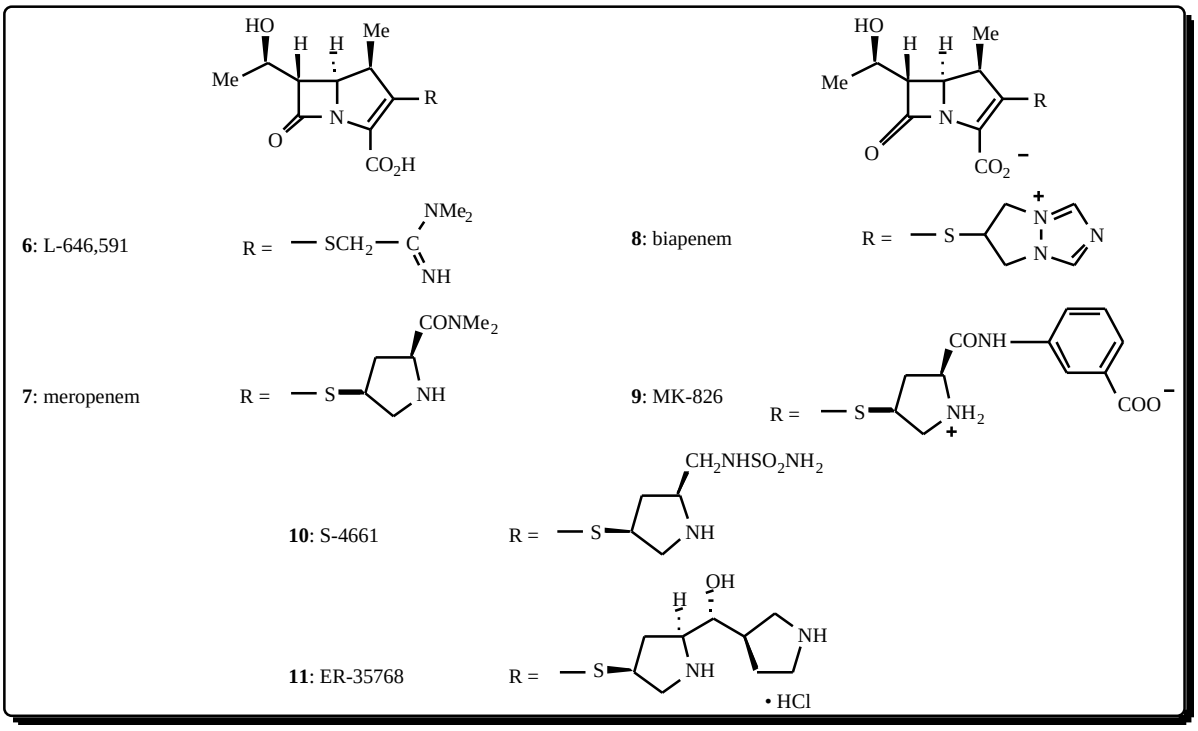
Since the discovery of thienamycin (**1**) in 1976, carbapenem compounds have provided a new generation of β-lactam antibiotics highly potent against a broad range of bacterial species [1-4]. Compound **1,** however, could not be marketed due to chemical and biological instability. To overcome these problems, many groups started to develop stable compounds and ways of synthesizing thienamycin because enzymatic production was not effective. Under these circumstances, imipenem (**2**) containing cilastatin (**4**) as an inhibitor of renal dehydropeptidase-I (DHP-I) was marketed by Merck & Co., Inc. Next, the Sankyo group marketed panipenem (**3**) containing betamipron (**5**) for the alleviation of nephrotoxicity.

In 1984, the Merck research group reported an attractive 1β-methylcarbapenem (**6**) [5]. Compound (**6**) had potential as a candidate for a new generation of antibiotics because it could directly resist metabolism by renal DHP-I without additives like cilastatin (**4**). The discovery of **6** accelerated the development of stereoselective carbon-carbon bond formation methods for the construction of chiral C-1 on 1β-substituted carbapenems [5-30, 42]. From these studies, meropenem (**7**) developed by the Sumitomo group was marketed as the first 1β-methylcarbapenem. After that,



*Address correspondence to this author at the Medical Research Laboratories, Wyeth Lederle (Japan) Ltd., 1-6-34, Kashiwa-cho, Shiki-shi, Saitama 353-8511, Japan; E-mail: KumagaT@labs.wyeth.com

1568-0126/02 $35.00+.00

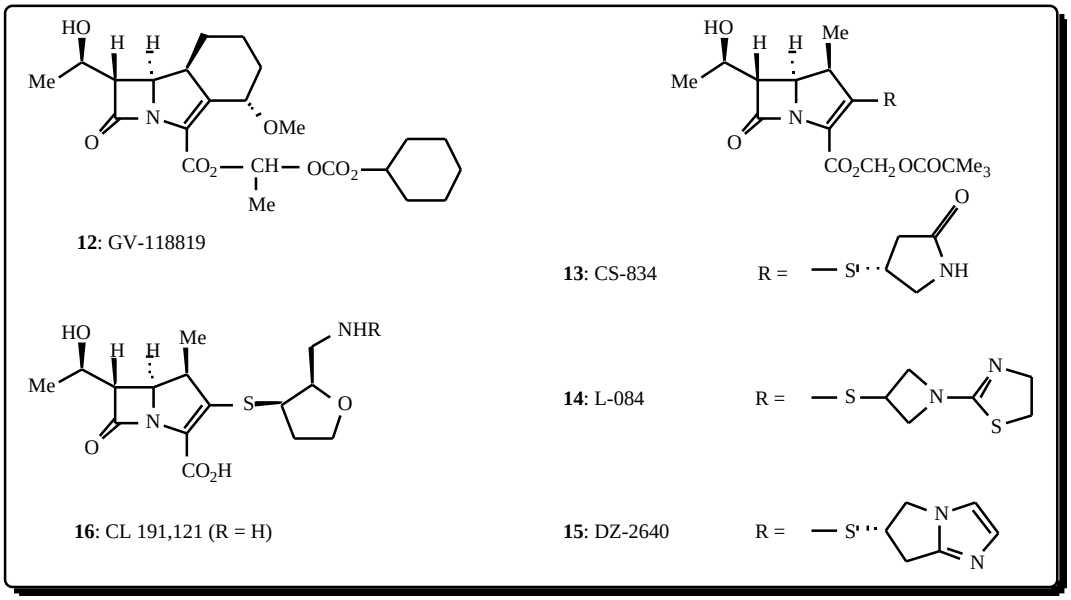


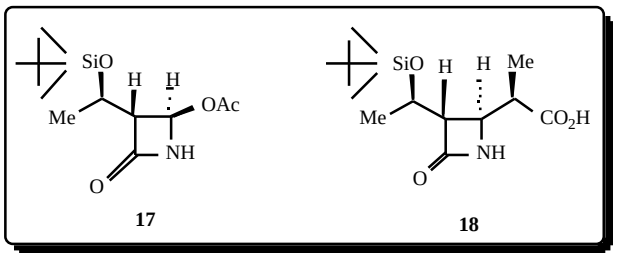
biapenem (**8**), MK-826 (**9**), S-4661 (**10**), and ER-35768 (**11**) underwent clinical trials [31-41]. All these compounds are for parenteral use.

Carbapenem compounds have long been considered unstable even in neutral conditions, much less in gastric juice and/or intestinal juice. However, recently, orally active 1β-methylcarbapenems including tricyclic carbapenems have been reported. Some of them, GV-118819 (**12**), CS-834 (**13**), L-084 (**14**), and DZ-2640 (**15**), are undergoing clinical trials and their pharmacokinetics in human have been demonstrated. In addition, CL 191,121 (**16**) and its derivatives **47**, **48, 49** have been undergoing preclinical studies. This review focuses on oral 1β-methylcarbapenems.

THE SYNTHESIS OF β-METHYLAZETIDIN-2-ONE

Carbapenem chemistry advanced rapidly with the development of practical methods of synthesizing 4-acetoxyazetidin-2-one (**17**) and β-methylazetidine-2-one (**18**) in the 1980s. With the establishment of a method of producing **6** by Shih *et al*. in 1984 [5], many research groups started studying highly stereoselective synthesis of **18** which





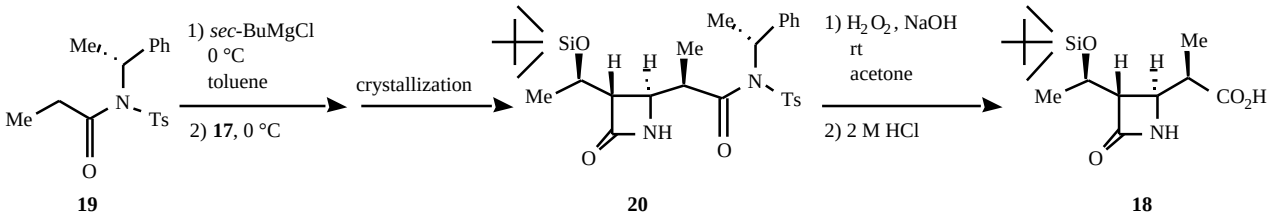
17 **18**

is a key intermediate for new 1β-methylcarbapenem antibiotics. The Merck group and ourselves reported on a highly diastereoselective alkylation at the C-4 position of 4-acetoxyazetidin-2-one (**17**) [7, 8]. Since then, effective and industrial ways to prepare **17** and **18** have been reported [42, 43, 44].

Recently, the Takasago group developed an aldol type reaction from **17** to **18** using magnesium enolate of chiral propanoyl sulfone amide (**19**) (Fig. **1**) [45].

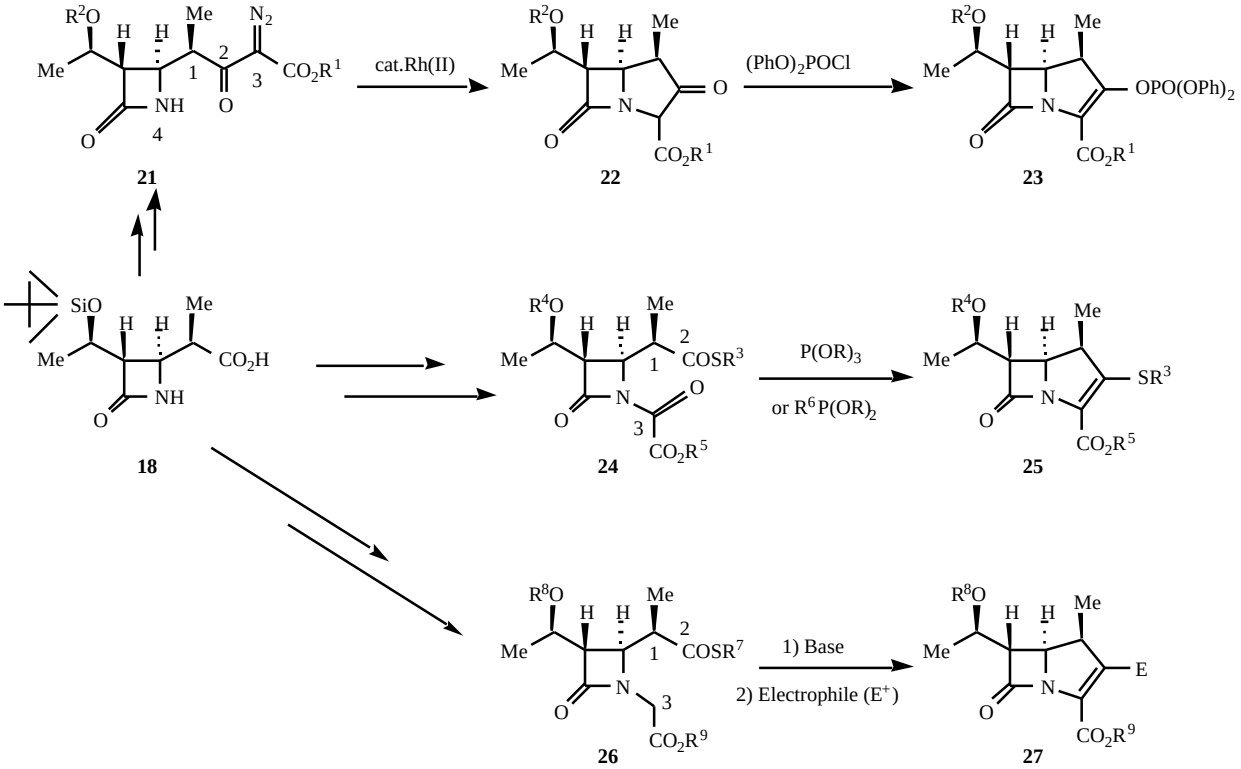
CONSTRUCTION OF A 1β-METHYLCARBAPENEM SKELETON

The formation of a 1β-methylcarbapenem skeleton from **18** has been accomplished by three different approaches (Fig. **2**). The intramolecular carbene insertion reaction, Wittig type reaction, and Dieckmann type reaction. First, a C3-N4 bond was formed by the intramolecular carbene insertion of diazo compound (**21**) in the presence of catalytic rhodium complex [5]. In 1992, we succeeded in preparing **23** (R^1 = *p*-nitrobenzyl) as crystals which are stable and a useful starting material for exploration of novel 1β-methylcarbapenem



19 **20** **18**

Fig. (1).



21 **22** **23** **18** **24** **25** **26** **27**

Fig. (2).

compounds [31]. Second, a C2-C3 bond formation was achieved by an intramolecular Wittig type reaction of compound (**24**) with the phosphite [46, 47, 48], and third, a Dieckmann type reaction of compound (**26**) with base was reported [49, 50]. Each compound, **21**, **24**, and **26**, is an important intermediate in the construction of the 1β-methylcarbapenem skeleton [5, 50-56].

Recently, a C3-N4 bond formation utilizing iodonium ylide and C2-C3 bond formation using Eschenmoser sulfide contraction were reported (Fig. **3**). Interesting results were obtained from the C3-N4 bond formation by the carbene insertion reaction using iodonium ylide. The use of an acidic catalyst in this reaction dominantly gave the 3*S*-form of **29** (94% yield). On the other hand, the use of a rhodium catalyst dominantly gave the 3*R*-form of **29** (86% yield) [57]. Regarding the C2-C3 bond formation, thiazinone (**30**) was used as a key intermediate to obtain **31** [58].

CONSTRUCTION OF THE TRICYCLIC CARBAPENEM SKELETON

Tricyclic carbapenems, which have a broad spectrum of activity against gram-positive and gram-negative bacteria and good stability in the presence of human DHP-I, were discovered by the Glaxo Welcome research group. GV 104326 (**35**), whose prodrug ester is undergoing clinical trials, was selected as a clinical candidate based on the structure-activity relationship [59, 60].

Highly diastereoselective synthesis of a key intermediate (**34**) for the construction of the tricyclic carbapenem skeleton has been achieved by the reaction of acetoxyazetidin-2-one (**17**) with homochiral cyclohexenyl boranes (**32**), cyclohex-2-enyldimethylsilyl chloride (**36**), or racemic β-ketoester (**38**) (Fig. **4**) [60, 61, 62].

As a further study of the tricyclic carbapenems, some thia- or oxa- or aza- analogs containing a sulfur, oxygen, or nitrogen atom in the cyclohexane ring have also been synthesized (Fig. **5**) and their antibacterial activities have been reported [64, 65, 66, 67].

DEVELOPMENT OF ORAL CARBAPENEMS

Since the discovery of thienamycin in 1976, numerous carbapenems have been developed for parenteral use, but not for oral administration because carbapenems have been considered unstable even under neutral conditions. In addition, β-lactam antibiotics are known to be difficult to absorb from the intestine.

In general, oral drugs are absorbed by either passive transport through phospholipid membranes or active transport through a carrier mechanism. Recently, oral carbapenems with a double ester or a peptidic structure which are chemically and biologically stable have been reported.

1. GV-118819 (12)

This is the first tricyclic carbapenem and has been developed as a prodrug ester by the Glaxo Welcome group. The structure-activity relationships of GV-104326 (**35**) and its related compound have been disclosed [60]. Some of the results are shown in Table **1**.

GV-104326 (**35**) showed a broad antibacterial spectrum with high potency, resistance to β-lactamases and good stability in the presence of renal dehydropeptidase-I. Comparative MICs were determined for **35** against 415 clinical isolates. The antibacterial activity against gram-

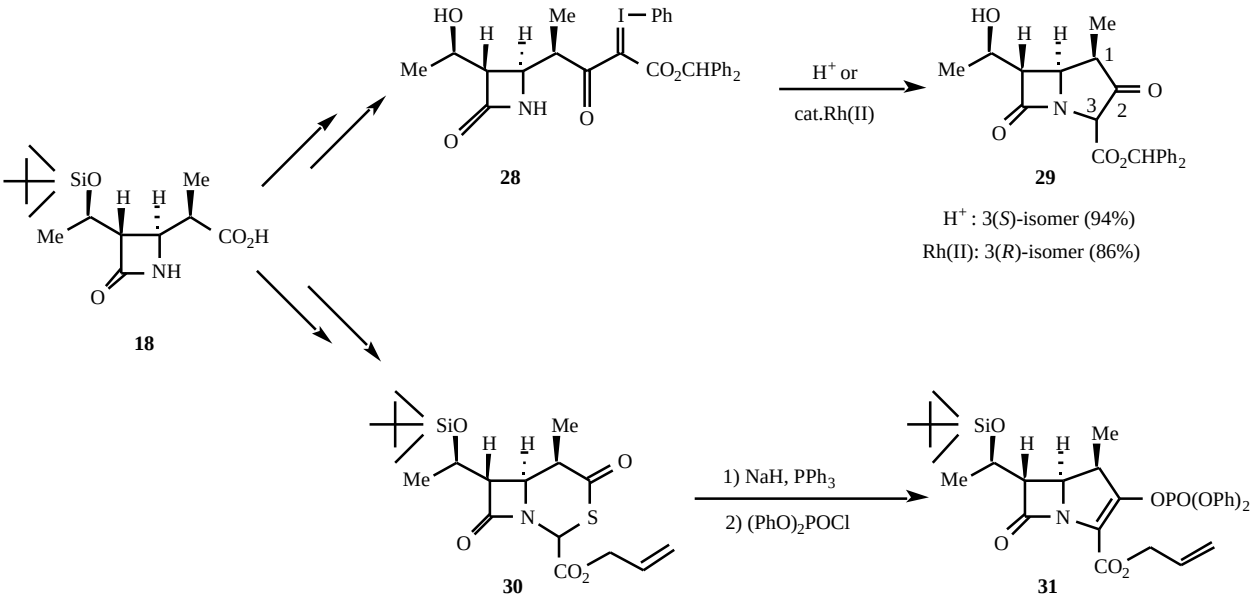
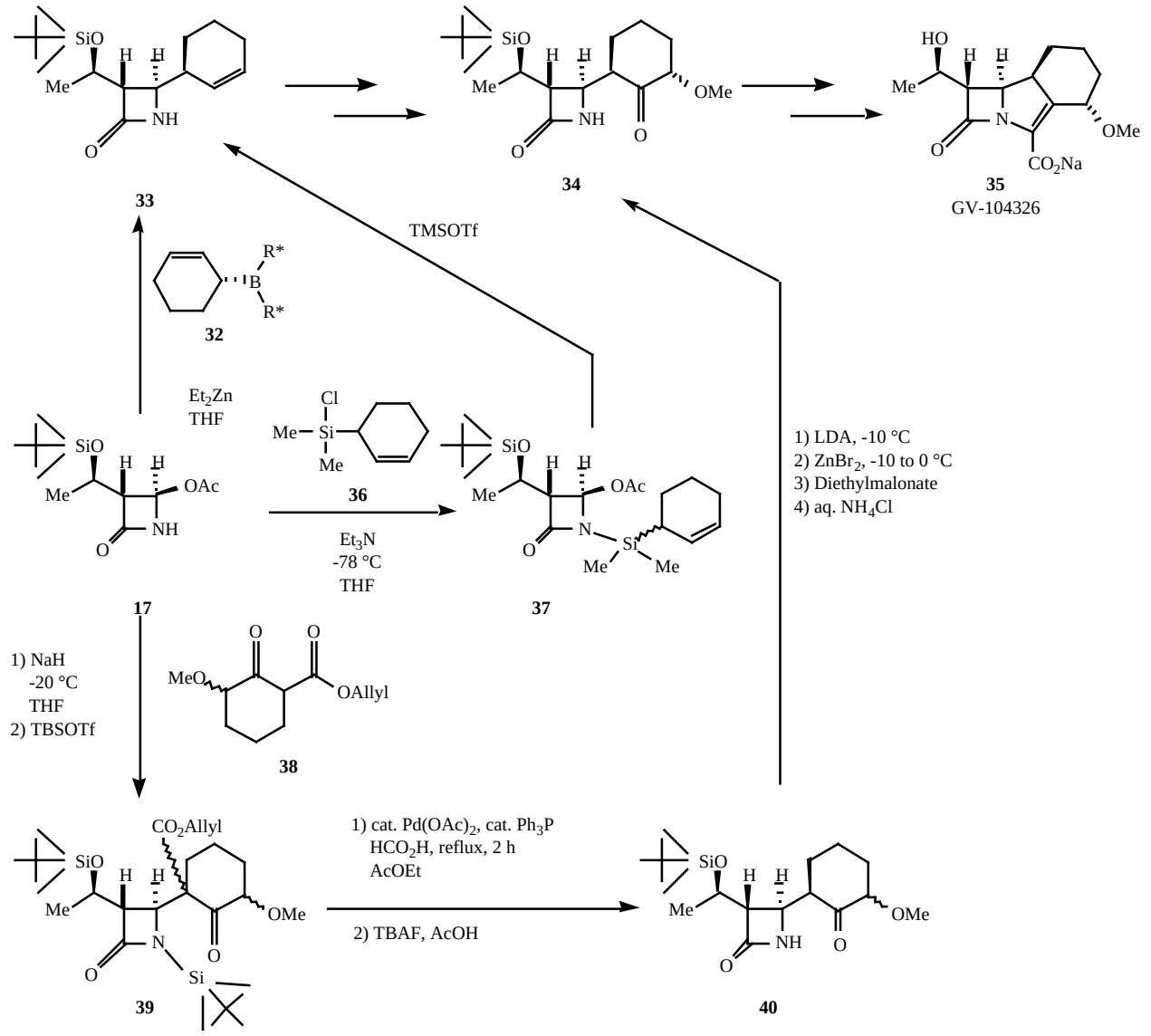


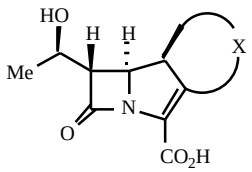
Fig. (3).



R*: isopinocampheyl from *S*-pinene

Fig. (4).

positive bacteria of **35** was slightly inferior to that of imipenem. Against gram-negative bacteria except *P. aeruginosa*, **35** possessed activity similar to imipenem. **35** was resistant to clinically relevant β-lactamases and was lethal to susceptible bacteria. **35** showed binding affinity for PBP 2 and 4 of *S. aureus* and for PBP 1a and 2 of *E. coli* [59].



X = O or S or NR

Fig. (5).

The pharmacokinetics of GV-118819 (**12**) following single oral administration at two dose levels to six healthy male volunteers have been reported [63]. Mean peak

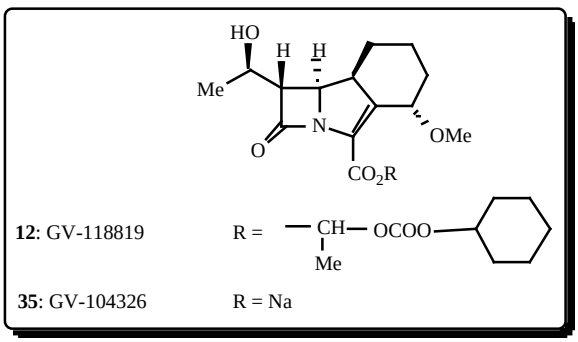
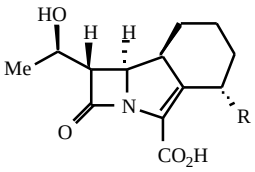


Table 1. Antimicrobial Activities (MIC : μg/ml)[a)]



Organism \ R	OMe	SMe	SOMe	NHMe	Imipenem
S. aureus	0.2	0.01	0.1	0.2	0.06
E. coli DC 0	0.5	1.5	0.5	2	0.5
E. coli DC 2 (TEM 1)[b)]	0.2	0.03	1	0.5	0.5
P. aeruginosa	32	32	16	4	4
C. perfringens 615	0.03	0.02	0.1	0.5	0.1
B. fragilis 2017	0.5	0.02	0.2	2	0.06

a) Minimal inhibitory concentrations determined by the microdilution method using Mueller-Hinton broth
b) β-Lactamase producing strain

concentrations of **35** in plasma of 0.77 and 2.47 μg/ml were reached at 1.1 and 2.0 h after dose of 125 and 500 mg as the equivalent of **35**, respectively. The mean half-lives in plasma were 1.33 and 1.97 h for the 125 and 500 mg doses, respectively. The mean recovery in urine was greater after 500 mg (24.2%) than 125 mg (18.4%) of **35**.

2. CS-834 (13)

This compound has been developed by the Sankyo group and is now in clinical trials. They found that R-83201 (**42**) had a good balance of antibacterial activity and biological stability. They also evaluated the urinary recovery of some prodrug esters of R-83201 (**42**) after oral administration in mice. Among them, two prodrug esters of **42**, the pivaloyloxymethyl ester (**13**) and the 1-methylcyclohexylcarbonyloxymethyl ester (**43**), exhibited excellent urinary recoveries of 47% and 55%, respectively. The pharmacokinetics of these two compounds in dogs after oral administration were compared to find the best prodrug ester (Table **2**) [68]. Then, the chemical stability of CS-834 was confirmed to be good in a neutral phosphate buffer solution (degradation rate constant: 0.031 at pH 6.86) [69]. Finally CS-834 was selected for further evaluation.

CS-834 (**13**) was administered orally for an evaluation of safety and pharmacokinetics to healthy male volunteers at single doses of 50, 100, 200, and 400 mg and at a multiple dose of 150 mg three times a day for 7 days. In the fasted state, the concentration of R-95867 (**41**) in plasma reached maximum levels from 1.1 to 1.7 h following the oral administration of CS-834. Maximum concentrations of R-95867 (**41**) in plasma of 0.51, 0.97, 1.59, and 2.51 μg/ml were attained after administration of CS-834 (**13**) at doses of 50, 100, 200, and 400 mg, respectively. The half-lives were about 0.7 h. The AUCs were proportional to the doses in the range from 50 to 400 mg. The cumulative urinary excretion ranged from 27 to 34% of the dose until 24 h after the drug administration. No influence of food intake on the pharmacokinetics of R-95867 (**41**) was observed.

The pharmacokinetics in the multiple dose study (150 mg three times a day for 7 days) were almost the same as those obtained in the single dose study [70].

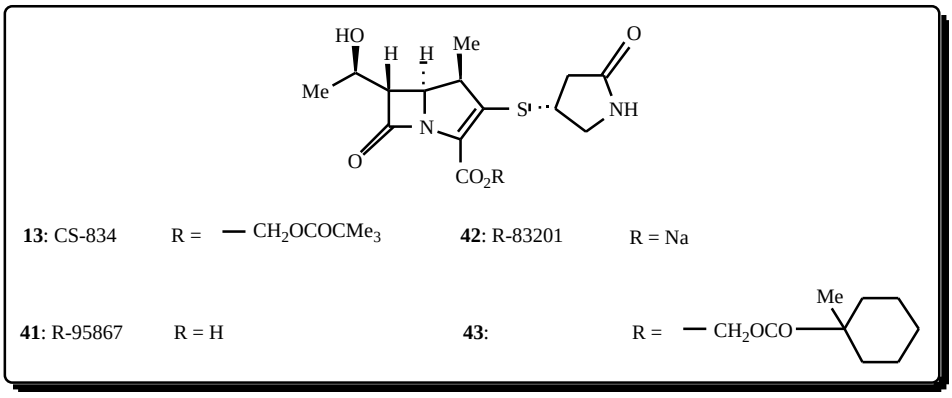
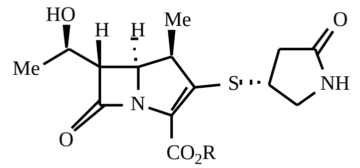
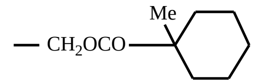
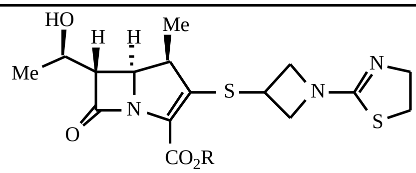


Table 2. Pharmacokinetic Parameters at a Dose of 10 mg/kg as the Equivalent of R-83201 (41) in Beagle Dogs



R	Na	— $CH_2OCOCMe_3$	
Administration	iv	oral	oral
Cmax (μg/ml)	38.4	6.1	2.6
Tmax (h)	——	1.00	0.83
T1/2 (h)	0.75	0.90	0.94
AUC (μg• hr/ml)	26.3	13.1	6.3
Absolute bioavailability (%)	100	50	24



14: L-084 R = — $CH_2OCOCMe_3$

44: L-036 R = H

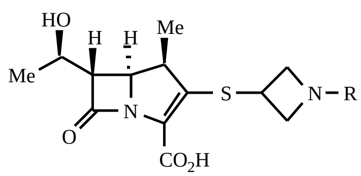
3. L-084 (14)

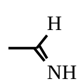
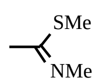
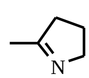
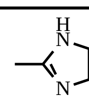
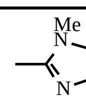
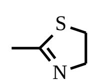
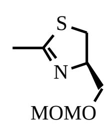
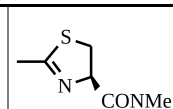
We discovered a novel and characteristic 1β-methylcarbapenem, L-084 (**14**), for oral administration. L-084 (**14**) and L-036 (**44**), the active form of L-084, have many advantages over other β-lactam compounds, especially in chemical and biological stability, antibacterial activity, and absorption ratio. L-084 is undergoing clinical trials.

3-1. Structure-Activity Relationships [71]

For the purpose of developing an oral carbapenem having unique characteristics, several kinds of compounds were synthesized in conventional ways and evaluated for their activity. The 1β-methylcarbapenems possessing an *N*-substituted azetidinylthio group as the C-2 side chain showed excellent antibacterial activity against gram-positive and gram-negative bacteria except *Pseudomonas aeruginosa* (Table **3**). The antibacterial activity of L-036 (**44**) was superior to that of related compounds.

Table 3. Antimicrobial Activity of L-036 and the Related Compounds (MIC: μg/ml)



Organism \ R						 (L-03 6)		
S. aureus 209P	0.2	0.1	0.025	0.025	0.025	0.013	0.05	0.1
S. pyogenes Cook	——	0.013	<0.006	<0.006	<0.006	<0.006	<0.006	0.013
E. coli NIHJ JC-2	0.025	0.05	0.025	0.025	0.025	0.013	0.05	0.025
K. pneumoniae PCI 602	0.025	0.025	0.05	0.05	0.1	0.013	0.013	0.025
S. marcescens 1184	0.05	0.1	0.1	0.1	——	0.05	0.39	0.2
P. aeruginosa PAO 1	3.13	25	6.25	3.13	12.5	12.5	100	50

3-2. Pharmacokinetics of Prodrug Esters of L-036 in Animals

In order to optimize the oral absorption of L-036 (**44**), various prodrug esters were prepared in conventional ways [68, 71] and were orally administered to rats (Table **4**). L-084 (**14**) was selected for further evaluation because of its chemical and biological stability and high bioavailability in animals.

3-3. Chemical and Biological Properties of L-084 and L-036

The conformation of the C6-hydroxyethyl group of L-036 (**44**) determined by X-ray analysis is similar to that of biapenem (**8**) developed for parenteral use. Interestingly, this conformation is clearly different from those of imipenem and meropenem [72, 73, 74]. It is not clear yet what effect this conformational difference has on each compound.

L-084 (**14**) in solution is most stable at pH 5 (degradation rate constant: 0.022). Even at pH 4, however, L-084 is very stable (degradation rate constant: 0.023). L-036 (**44**), meanwhile, is most stable in solution at pH 6 (degradation rate constant: 0.011). These facts indicate that L-084 would be fairly stable during passage through the stomach and that L-036 delivered to the infection focus, considered to be weakly acidic, would be very effective due to its good stability in a weak acid solution.

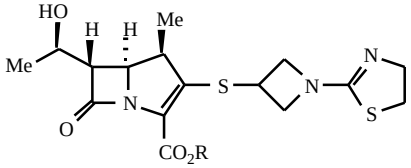
The resistance to human renal dehydropeptidase-I is higher than that of meropenem (**7**) which is a 1β-methylcarbapenem.

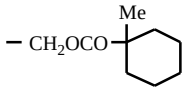
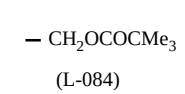
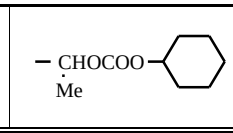
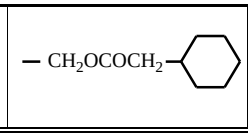
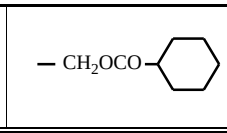
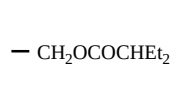
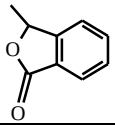
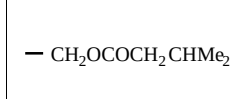
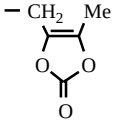
3-4. In Vitro Antibacterial Activity of L-036, an Active Metabolite of L-084 [75]

Antibacterial activities of L-036 (**44**) against clinical isolates of gram-positive and gram–negative bacteria were examined. The clinical isolates of bacteria were *S. aureus* (n = 106, MSSA; 53, MRSA; 53), *S. epidermidis* (n = 52), *S. pneumoniae* (n = 52, PSSP; 24, PRSP; 28), *S. pyogenes* (n = 19), *E. coli* (n = 50), *K. pneumoniae* (n = 53), *M. catarrhalis* (n = 53), *E. cloacae* (n = 53), *P. mirabilis* (n = 53), *S. marcescens* (n = 54), and *P. aeruginosa* (n = 5). The activities of L-036 against clinical isolates of gram-positive bacteria were slightly superior to those of imipenem. On the other hand, the activities against clinical isolates of gram-negative bacteria were stronger than those of levofloxacin except for *H. influenzae* and *P. aeruginosa*. The activity of L-036 against *H. influenzae* was stronger than that of imipenem.

L-036 also showed potent activities against various β-lactamase-producing strains excluding carbapenemase producers. L-036 exhibited high binding affinities for PBP 1A, -1B, -2A/2X, -2B, and 3 of penicillin resistant *S. pneumoniae* (PRSP) and for PBP 1B, -2, -3A, and -3B of *H. influenzae*.

Table 4. Pharmacokinetic Parameters of Various Prodrug Esters of L-036 (44**) After Oral Administration to Rats at a Dose of 20 mg/kg as L-036**



R					
Cmax[1)]	15.3	14.8	13.6	12.3	10.1
AUC[1)]	11.5	10.7	10.1	9.7	8.3
BA (%)[2)]	41.2	38.1	36.0	34.9	29.6
R					**H** **(L-036)**
Cmax[1)]	9.9	7.3	5.7	2	0.3
AUC[1)]	6.8	5.5	3.7	1.6	0.2
BA (%)[2)]	24.2	19.5	13.1	5.8	0.8

1) Cmax (μg / ml), AUC (μg• h/ml)
2) Bioavailability (BA) was caluclated from AUC (28.0 μg• h/ml) after i.v. administration of L-036 at a dose of 20 mg / kg.

L-036 displayed significant postantibiotic sub-MIC activity *in vitro* against PRSP HSC-3 (6.0 h at one-forth the MIC) and *H. influenzae* LJ 5 (9.2 h at one-half the MIC).

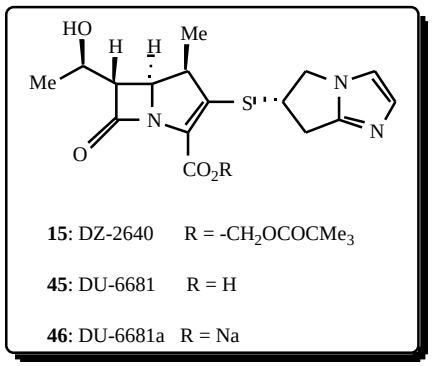
3-5. Pharmacokinetics of L-084 in Human [76]

L-084 (**14**) was administered orally to healthy male volunteers at single doses of 25, 50, 100, and 200 mg and at a multiple dose of 100 mg and 200 mg three times a day for 7 days as the equivalent of L-036 (**44**) to investigate its safety and pharmacokinetics. In addition, the effect of food intake on the absorption was examined at a dose of 75 mg. The mean maximum concentrations of L-036 in plasma (Cmax) ranged from 1.27 (25 mg dose) to 5.93 μg/ml (200 mg dose) and were reached from 0.5 to 0.7 h following the drug administration. The half-lives were from 0.3 to 0.5 h. The areas under the concentration-time curve (AUCs) were proportional to the doses in the range from 25 to 200 mg. The accumulative urinary recoveries (0 to 24 h) of L-036 were in the range of 54 to 73%. The level of the hydrolyzed product of the β-lactam ring of L-036 was about 10% in urine as an inactive metabolite. No effect of food intake was observed. The multiple-dose study showed no drug accumulation in the body. No significant adverse event was observed.

L-036 (**44**) reaches a fairly high Cmax quickly after oral administration of L-084 (**14**) which shows very high bioavailability, is excreted rapidly. Taking the long post antibiotic effect of L-036 into consideration, L-084 would afford the maximum effect at minimum amounts.

4. DZ-2640 (15)

This compound was found by the Dai-ichi group [77]. DU-6681 (**45**) having a chiral bicyclic imidazole ring as the C-2 substituent showed potent and broad antibacterial activity except against *P. aeruginosa*. The structure-activity relationships of the compounds having different bicyclic



imidazole ring systems and of their optical isomers shown in Fig. (**6**) were examined.

It was observed that the bicyclic imidazole ring system attached to the C-2 position of 1β-methylcarbapenem influenced the stability in the presence of dehydropeptidase-I and the pharmacokinetics in rats after oral administration of each pivaloyloxymethyl ester (Table **5**).

After the selection of DU-6681 (**45**) based on these results, several prodrug esters were prepared in order to optimize the oral absorption (Table **6**). DZ-2640 (**15**), the pivaloyloxymethyl ester of DU-6681 (**45**), was then selected for further study.

The antibacterial activity of DU-6681a (**46**), sodium salt of a parent compound of DZ-2640 (**15**), against clinical isolates of gram-positive and gram-negative bacteria was studied [78]. The MIC_{90}s of DU-6681a for methicillin-susceptible *S. aureus* (MSSA, n = 27), methicillin-resistant *S. aureus* (MRSA, n = 19), and *S. epidermidis* (n = 22) were 0.01, 25, and 12.5 μg/ml, respectively. The MIC_{90}s for *S. pyogenes* (n = 25) and penicillin-susceptible (n = 18) and penicillin-resistant *S. pneumoniae* (n = 21) were 0.006, 0.025, and 0.20 μg/ml, respectively. The MIC_{90}s for *H.*

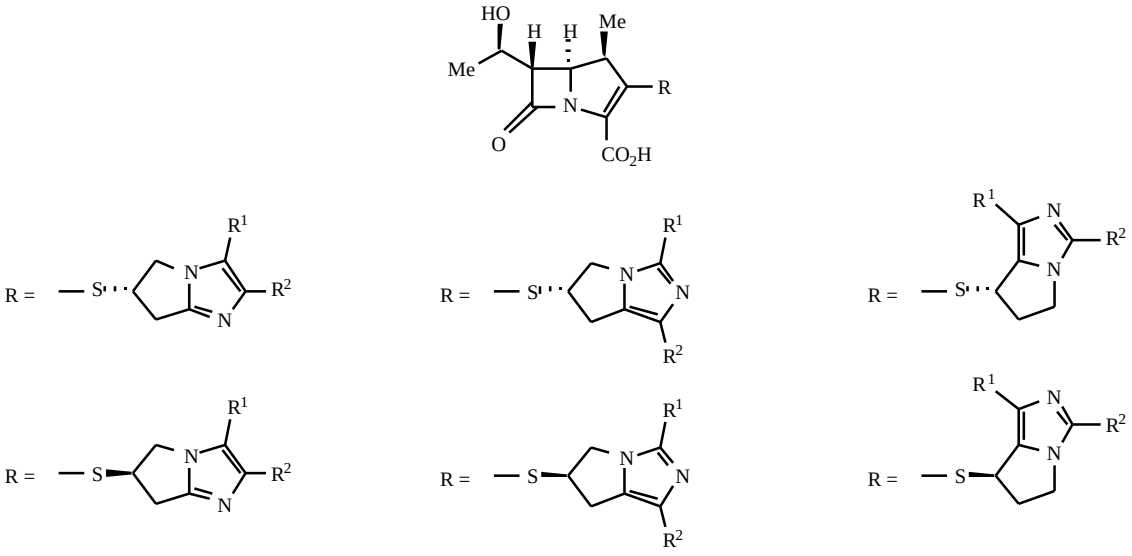
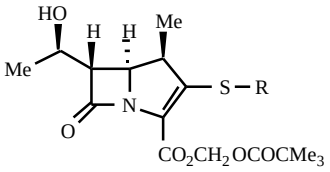
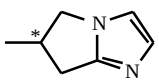
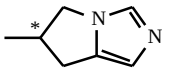
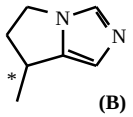


Fig. (6).

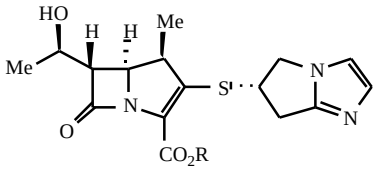
Table 5. Pharmacokinetic Parameters of Oral Carbapenems Having Bicyclic Imidazole Ring System as C-2 Substituent After Administration to Rats at a Dose of 20mg/kg as the Parent Compounds



R isomer	 (*S*) **DZ-2640**	(*R*)	 (*S*)	(*R*)	 (A)	(B)
C max (μg/ml)	5.23	3.48	3.83	2.20	19.98	7.00
AUC (μg• h/ml)	4.48	2.77	2.98	1.89	17.44	4.09
Urinary Recovery (% of dose)	24.6	11.2	15.8	12.2	18.5	14.9
DHP-I [a] stability b of parent compound	6	12	0.3	1	10	2

a) Partial purified renal dehydropeptidase-I of swine
b) Relative hydrolysis rate (imipenem = 100)

Table 6. Pharmacokinetic Parameters of Various Prodrug Esters of DU-6681 (45) After Oral Administration to Rats at a Dose of 20mg/kg as DU-6681 (45).



R	– $CH_2OCOCMe_3$ **DZ-2640**	**DZ-2640 (HCl salt)**	– CH_2OCOMe	– CHOCOOCHEt$_2$ Me **(HCl salt)**	– CHOCOO Me **(HCl salt)**	– CH_2 Me **(HCl salt)**
Cmax (μg/ml)	5.23	7.27	1.69	7.66	3.39	0.59
AUC (μg• h/ml)	4.84	5.04	1.23	5.06	3.41	0.22
Urinary Recovery (% of dose)	24.6	30.4	7.1	22.2	17.3	2.8

influenzae including β-lactamase-producing strains (n = 38) was 0.02 μg/ml. DU-6681a (**46**) was stable on exposure to various types of β-lactamases except *S. maltophilia* type 3 enzyme and showed potent antibacterial activity against β-lactamase-producing strains except *S. maltophilia* and *P. aeruginosa*. In addition, DU-6681a (**46**) is much more resistant to renal dehydropeptidase-I than imipenem.

The pharmacokinetics of DZ-2640 (**15**) in the mouse, rat, dog, and monkey were investigated and a species difference was observed in the Cmax and excretion rate (the mouse had the highest Cmax and the dog the lowest urinary recovery rate) [79].

The pharmacokinetics of DZ-2640 (**15**) in healthy volunteers were investigated after administration of single doses at 25, 50, 100, 200, and 400 mg (as the equivalent of DU-6681) in the fasted state. The effect of food intake on the bioavailability of DZ-2640 was examined [80]. The mean maximum concentrations of DU-6681 in plasma (Cmax) ranged from 0.263 μg/ml (25 mg dose) to 2.489 μg/ml (400 mg dose) and were reached within 1.5 h of the drug

administration. After reaching the Cmax, plasma concentrations of DU-6681 (**45**) declined in a monophasic manner with half-lives of 0.47 h to 0.89 h. The area under the concentration-time curve (AUC) and Cmax increased almost linearly with the doses up to 200 mg. On administration of 400 mg, the AUC and Cmax did not increase proportionally. The cumulative urinary recoveries (0 to 24 h) were in the range of 32 to 45%. Food intake significantly decreased the AUC, but there was no effect on the Cmax, Tmax, half-life, or cumulative urinary recovery.

5. CL 191,121 (16) and the Peptidic Derivatives

This study has been done by the Wyeth-Ayerst group and is in the pre-clinical stage.

The compound, CL 191,121 (**16**), possessing an aminomethyltertahydrofuranylthio group as the C-2 substituent on 1β-methylcarbapenem, has a broad spectrum and potent antibacterial activities [81, 82]. It was found that CL 191,121 (**16**) demonstrated moderate oral activity against an *E. coli* infection in mice [82, 83]. In order to improve the bioavailability of CL 191,121 (**16**), they made use of a peptide-mediated transport system and synthesized various compounds in which amino acids were introduced to the aminomethyltetrahydrofuranyl side chain at the C-2 position [84].

The resulting peptidic prodrugs with L-amino acids showed improved efficacy after oral administration in mice. Peak levels of 4.8, 7.4, and 9.2 μg/ml of CL 191,121 were observed in the serum of mice given oral doses of 20 mg/kg of 121-Ala (**47**), 121-Val (**48**), and 121-Ile (**49**), respectively. The levels of peptidic carbapenems, **47**, **48**, and **49**, in serum were below the limit of detection at all time points after the oral administration of an equivalent dose of CL 191,121 (**16**). In contrast, the oral activity of D-amino acid derivatives was less than that of CL 191,121. From these results, it was concluded that D-amino acid derivatives of **16** could not be absorbed and L-amino acid derivatives of **16** increase the bioavailability [83].

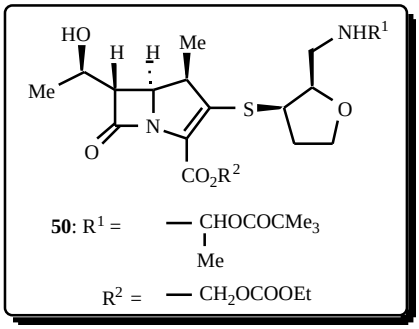
CL 191,121 (**16**), 121-Ala (**47**), 121-Val (**48**), and 121-Ile (**49**) exhibited good resistance to hydrolysis by renal dehydropeptidases of the mouse, rat, hog, and human [85].

Double ester prodrugs of CL 191,121 (**16**) were also prepared in order to facilitate absorption through the phospholipid membranes by eliminating the ionic nature and increasing the lipophilicity of **16**. The bis-double ester derivatives demonstrated a more enhanced oral activity than the mono-double ester derivatives. The oral activity of the bis-double ester derivative (**50**: R^1 = -$CH(CH_3)OCO(CH_3)_3$, R^2 = -$CH_2OCO_2CH_2CH_3$) was the same as that of 121-Val (**48**), peptidic prodrug [86]. Further progress in the development of peptidic prodrugs of **16** is expected.

Patents for bis-double ester derivatives of meropenem (**7**) were published in 1998 and 1999 [87]. To our knowledge, there are no reports available on these compounds.

CONCLUSION

An orally active carbapenem has been awaited since the discovery of thienamycin in 1976. However, many problems



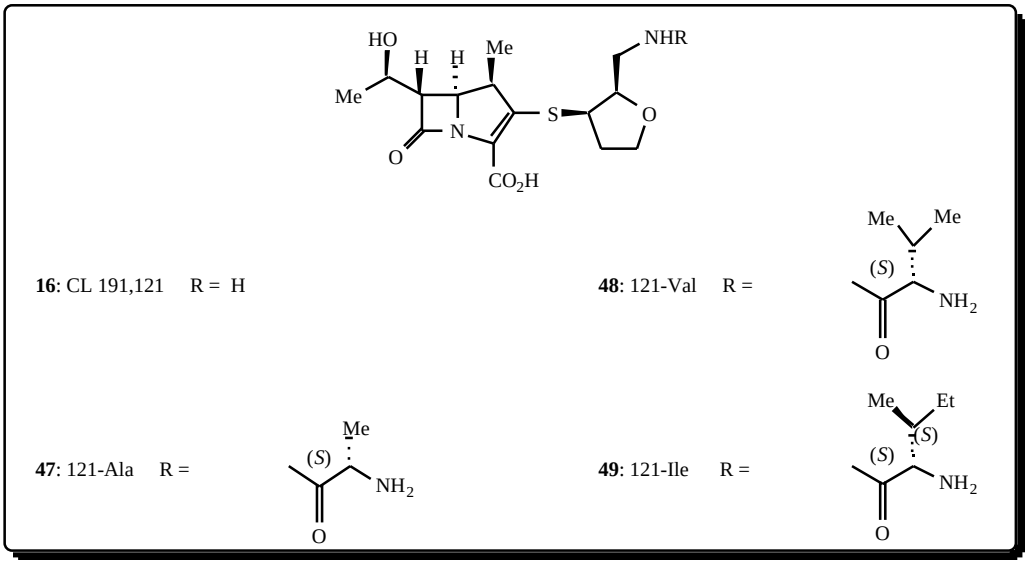


Table 7. Pharmacokinetic Parameters After Oral Administration to Human

	Dose (mg)[1)]	Cmax (μg/ml)	Tmax (h)	$t_{1/2}$(h)	$AUC_{0\text{-}00}$ (μg• hr/ml)	Urinary recovery(%)
GV-118819 (**12**)	125	0.77	2.0	1.33	1.76	18.4
CS-834 (**13**)	71.8	0.97	1.25	0.73	1.91	32.5
L-084 (**14**)	100	4.06	0.5	0.4	3.47	72
DZ-2640 (**15**)	100	1.0	1.38	0.69	1.5	37.5

1) Esters were orally administered at a dose shown here as each active form.

had to be solved, such as chemical stability, bioavailability, etc.

Recently, 1β-methylcarbapenems without these problems have been developed and their chemical and biological properties, as well as pharmacokinetics in laboratory animals and humans reported. Table **7** shows the pharmacokinetic parameters after oral administration to humans reported to date. However, no orally active carbapenem is as yet on the market. The first thing to be done is to improve the chemical stability. The second thing is to improve the bioavailability. The last thing is to establish a method of low cost production. The search for an orally active carbapenem is still in the initial stage, and great progress is hoped for in the future.

ACKNOWLEDGEMENT

The authors wish to thank Professor Y. Nagao, the University of Tokushima, for helpful discussion and advice.

REFERENCES

[1] Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B. *16th Intersci. Conf. Antimicrob. Agents Chemother.*, **1976**, Abst. 227.

[2] Kropp, H.; Kahan, J. S.; Kahan, F. M.; Sandorf, J.; Darland, G.; Birnbaum, J. *16th Intersci. Conf. Antimicrob. Agents Chemother.*, **1976**, Abst. 228.

[3] Schönberg, G. A.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.*, **1978**, *106*, 6491.

[4] Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.*, **1979**, *32*, 1.

[5] Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles*, **1984**, *21*, 29.

[6] Shih, D. H.; Cama, L.; Christensen, B. G. *Tetrahedron Lett.*, **1985**, *26*, 587.

[7] Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.*, **1986**, *108*, 4673.

[8] Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.*, **1986**, *108*, 4675.

[9] Iimori, T.; Shibasaki, M. *Tetrahedron Lett.*, **1986**, *27*, 2149.

[10] Shibata, T.; Iino, K.; Tanaka, T.; Hashimoto, T.; Kameyama, Y.; Sugimura, Y. *Tetrahedron Lett.*, **1985**, *26*, 4739.

[11] Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.*, **1985**, 1343.

[12] Deziel, R.; Favreau, D. *Tetrahedron Lett.*, **1986**, *27*, 5687.

[13] Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S. *Tetrahedron Lett.*,**1986**, *27*, 6241.

[14] Hatanaka, M. *Tetrahedron Lett.*, **1987**, *28*, 83.

[15] Kim, C. U.; Luh, B.; Partyka, R. A. *Tetrahedron Lett.*, **1987**, *28*, 507.

[16] Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.*, **1987**, *28*, 1857.

[17] Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.*, **1987**, *28*, 6141.

[18] Ito, Y.; Terashima, S. *Tetrahedron Lett.*, **1987**, *28*, 6625.

[19] Fuentes, L. M.; Shinkai, I.; King, A.; Puriek, R.; Reamer, R. A.; Schmitt, S. M.; Cama, L.; Christensen, B. G. *J. Org. Chem.*, **1987**, *52*, 2563.

[20] Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.*, **1987**, *52*, 3174.

[21] Shirai, F.; Nakai, T. *J. Org. Chem.*, **1987**, *52*, 5491.

[22] Ihara, M.; Takahashi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc. Chem. Comun.*, **1988**, 9.

[23] Deziel, R.; Endo, M. *Tetrahedron Lett.*, **1988**, *29*, 61.

[24] Bayles, R.; Flynn, A. P.; Galt, R. H. B.; Kirby, S.; Turner, R. W. *Tetrahedron Lett.*, **1988**, *29*, 6345.

[25] Shirai, F.; Nakai, T. *Tetrahedron Lett.*, **1988**, *29*, 6461.

[26] Endo, M.; Droghini, R. *Can. J. Chem.*, **1988**, *66*, 1400.

[27] Martel, A.; Daris, J. P.; Bachand, C.; Corbeil, J.; Menard, M. *Can. J. Chem.*, **1988**, *66*, 1537.

[28] Udodong, U. E.; Fraser-Reid, B. *J. Org. Chem.*, **1988**, *53*, 2131.

[29] Sowin, T. J.; Meyers, A. I. *J. Org. Chem.*, **1988**, *53*, 4154.

[30] Kaga, H.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.*, **1989**, *30*, 113.

[31] Nagao, Y.; Nagase, Y.; Kumagai, T.; Matsunaga, H.; Abe, T.; Shimada, O.; Hayashi, T.; Inoue, Y. *J. Org. Chem.*, **1992**, *57*, 4243.

[32] Petersen, P. J.; Jacobus, N. V.; Weiss, W. J.; Testa, R. T. *Antimicrob. Agents Chemother.*, **1991**, *35*, 203.

[33] Catchpole, C. R.; Wise, R.; Thornber, D.; Andrews, J. M. *Antimicrob. Agents Chemother.*, **1992**, *36*, 1928.

[34] Neu, H.; Gu, J. W.; Frang, W.; Chin, N. X. *Antimicrob. Agents Chemother.*, **1992**, *36*, 1418.

[35] Wexler, H. M.; Molitoris, E.; Finegold, S. M. *J. Antimicrob. Chemother.*, **1994**, *33*, 629.

[36] Aldrige, K. E.; Morice, N.; Schiro, D. D. *Antimicrob. Agents Chemother.*, **1994**, *38*, 889.

[37] Ubukata, K.; Hikida, M.; Yoshida, M.; Nishiki, K.; Furukawa, Y.; Tashiro, K.; Konno, M.; Mitsuhashi, S. *Antimicrob. Agents Chemother.*, **1990**, *34*, 994.

[38] Iso, Y.; Irie, T.; Nishino, Y.; Motokawa, K.; Nishitani, Y. *J. Antibiot.*, **1996**, *49*, 199.

[39] Iso, Y.; Irie, T.; Iwaki, T.; Kii, M.; Sendo, Y.; Motokawa, K.; Nishitani, Y. *J. Antibiot.*, **1996**, *49*, 478.

[40] Ohba, F.; Nakamura-Kamijo, M.; Watanabe, N.; Katsu, K. *Antimicrob. Agents Chemother.*, **1997**, *41*, 298.

[41] Wong, B. K.; Bruhin, P. J.; Lin, J. H. *J. Pharm. Sci.*, **1999**, *88*, 277.

[42] Berks, A. H. *Tetrahedron*, **1996**, *52*, 331.

[43] Murayama, T.; Yoshida, A.; Kobayashi, T.; Miura, T. *Tetrahedron Lett.*, **1994**, *35*, 2271.

[44] Nozaki, K.; Li, W.; Horiuti, T.; Takaya, H.; Sato, T.; Yoshida, A.; Matsumura, K.; Kato, Y.; Imai, T.; Miura, T.; Kumobayashi, H. *J. Org. Chem.*, **1996**, *61*, 7658.

[45] Miura, T.; Murayama, T.; Yoshida, A.; Kobayashi, T. *Eur. Patent Appl.*, EP 974582, Jan. 26, **2000**.

[46] Yoshida, A.; Tajima, Y.; Takeda, N.; Oida, S. *Tetrahedron Lett.*, **1984**, *25*, 2793.

[47] Shibata, T.; Iino, K.; Tanaka, T.; Hashimoto, T.; Kameyama, Y.; Sugimura, Y. *Tetrahedron Lett.*, **1985**, *26*, 4739.

[48] Mori, M.; Oida, S. *Chem. Pharm. Bull.*, **2000**, *48*, 126.

[49] Sunagawa, M.; Sasaki, A.; Matsumura, H.; Goda, K.; Tamoto, K. *Chem. Pharm. Bull.*, **1994**, *42*, 1381.

[50] Seki, M.; Kondo, K.; Iwasaki, T. *Synlett.*, **1995**, 315.

[51] Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. *J. Med. Chem.*, **1987**, *30*, 871.

[52] Schmitt, S. M.; Salzmann, T. N.; Shih, D. H.; Christensen, B. G. *J. Antibiot.*, **1988**, *41*, 780.

[53] Sowin, T. J.; Meyers, A. I. *J. Org. Chem.*, **1988**, *53*, 4156.

[54] Deziel, R.; Favreau, D. *Tetrahedron Lett.*, **1989**, *30*, 1345.

[55] Shibata, T.; Sugimura, Y. *J. Antibiot.*, **1989**, *42*, 374.

[56] Salzmann, T. N.; Di Ninno, F. P.; Greenlee, M. L.; Guthikonda, R. N.; Quesada, M. L.; Schmitt, S. M.; Herrmann, J. J.; Woods, M. F. *Resent Advance in the Chemistry of* β*-Lactam Antibiotics* Ed.; Bentley, P. H.; Southgate, R. the Royal Society of Chemistry, London, **1989**, pp171.

[57] Kume, M.; Kubota, T.; Iso, Y. *Tetrahedron Lett.*, **1995**, *36*, 8043.

[58] Sakurai, O.; Ogiku, T.; Takahashi, M.; Horikawa, H.; Iwasaki, T. *Tetrahedron Lett.*, **1994**, *35*, 2187.

[59] Di Modugno, E.; Erbetti, I.; Ferrari, L.; Galassi, G.; Hammond, S. H.; Xerri, L. *Antimicrob. Agents Chemother.*, **1994**, *38*, 2362.

[60] Gaviraghi, G. *Eur. J. Med. Chem.*, **1995**, *30* (Suppl.), 467s.

[61] Bismara, C.; Di Fabio, R.; Donati, D.; Rossi, T.; Thomas, R. J. *Tetrahedron Lett.*, **1995**, *36*, 4283.

[62] Hanessian, S.; Rozema, M. J. *J. Am. Chem. Soc.*, **1996**, *118*, 9884.

[63] Wise, R.; Andrews, J. M.; Da Los, L.; Child, J.; Mortiboy, D. *Antimicrob. Agents Chemother.*, **1997**, *41*, 1761.

[64] Biondi, S.; Piga, E.; Rossi, T.; Vigelli, G. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 2061.

[65] Schmidt, G.; Schrock, W.; Endermann, R. *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 2193.

[66] Andreotti, D.; Rossi, T.; Marchioro, C. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 2589.

[67] Mori, M.; Somada, A.; Oida, S. *Chem. Pharm. Bull.*, **2000**, *48*, 716.

[68] Miyauchi, M.; Endo, R.; Hisaoka, M.; Yasuda, H.; Kawamoto, I. *J. Antibiot.*, **1997**, *50*, 429.

[69] Miyauchi, M.; Kanno, O.; Kawamoto, I. *J. Antibiot.*, **1997**, *50*, 794.

[70] Umemura, K.; Ikeda, Y.; Kondo, K.; Nakashima, M.; Naganuma, H.; Hisaoka, M.; Nishino, H.; Tajima, M. *Antimicrob. Agents Chemother.*, **1997**, *41*, 2664.

[71] Abe, T.; Hayashi, K.; Mihira, A.; Satoh, C.; Tamai, S.; Yamamoto, S.; Hikida, M.; Kumagai, T.; Kitamura, M. *38th Intersci. Conf. Antimicrob. Agents Chemother.* (Sep. 24-27, San Diego), **1998**, Abst. F-64.

[72] Ratcliffe, R. W.; Wildonger, K. J.; Michele, L. D.; Douglas, A. W.; Hajdu, R.; Goegelman, R. T.; Springer, J. P.; Hishfield, J. *J. Org. Chem.*, **1989**, *54*, 653.

[73] Yanagi, K.; Takeuchi, Y.; Sunagawa, M. *Acta Crystallogr.*, **1992**, *C48*, 1737.

[74] Kumagai, T.; Tamai, S.; Abe, T.; Matsunaga, H.; Hayashi, K.; Kishi, I.; Shiro, M.; Nagao, Y. *J. Org. Chem.*, **1998**, *63*, 8145.

[75] Hikida, M.; Itahashi, K.; Igarashi, A.; Shiba, T.; Kitamura, M. *Antimicrob. Agents Chemother*., **1999**, *43*, 2010.

[76] Yokokawa, M.; Yano, M.; Nakashima, M. *39th Intersci. Conf. Antimicrob. Agents Chemother.* (Sep. 26-29, San Francisco), **1999**, Abst. F-388.

[77] Nishi, T.; Ishida, Y.; Sugita, K.; Ohtsuka, M.; Takemura, M.; Hayakawa, I.; Hayano, T. *35th Intersci. Conf. Antimicrob. Agents Chemother*., **1995**, Abst. F-133.

[78] Tanaka, M.; Hohmura, M.; Nishi, T.; Sato, K.; Hayakawa, I. *Antimicrob. Agents Chemother*., **1997**, *41*, 1260.

[79] Aoki, H.; Sekiguchi, M.; Akahane, K.; Tsutomi, Y.; Korenaga, H.; Hayano, T.; Hayakawa, I. *35th Intersci. Conf. Antimicrob. Agents Chemother*., **1995**, Abst. F-135.

[80] Tanaka, M.; Kato, K.; Hakusui, H.; Murakami, Y.; Sato, K.; Ito, Y.; Kawamoto, K. *Antimicrob. Agents Chemother*., **2000**, *44*, 578.

[81] Lin, Y-I.; Bitha, P.; Sakya, S. M.; Strohmeyer, T. W.; Li, Z.; Lee, V. J.; Lang, S. A., Jr.; Yang, Y.; Bhachech, N.; Weiss, W. J.; Petersen, P. J.; Jacobus, N. V.; Bush, K.; Testa, R. T.; Tally, F. P. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1671.

[82] Weiss, W. J.; Petersen, P. J.; Jacobus, N. V.; Lin, Y-I.; Bitha, P.; Testa, R. T. *Antimicrob. Agents Chemother.*, **1999**, *43*, 454.

[83] Weiss, W. J.; Mikels, S. M.; Petersen, P. J.; Jacobus, N. V.; Bitha, P.; Lin, Y-I.; Testa, R. T. *Antimicrob. Agents Chemother*., **1999**, *43*, 460.

[84] Lin, Y-I.; Bitha, P.; Sakya, S. M.; Li, Z.; Lang, S. A., Jr.; Yang, Y.; Bhachech, N.; Weiss, W. J.; Petersen, P. J.; Jacobus, N. V.; Bush, K.; Testa, R. T. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1665.

[85] Yang, Y.; Testa, R. T.; Bhachech, N.; Rasmussen, B. A.; Bush, K. *Antimicrob. Agents Chemother*., **1999**, *43*, 2904.

[86] Lin, Y-I.; Bitha, P.; Li, Z.; Sakya, S. M.; Strohmeyer, T. W.; Lang, S. A., Jr.; Yang, Y.; Bhachech, N.; Weiss, W. J.; Petersen, P. J.; Jacobus, N. V.; Bush, K.; Testa, R. T. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1811.

[87] International Patent Publication No. WO 98/34936.