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Tomopenem

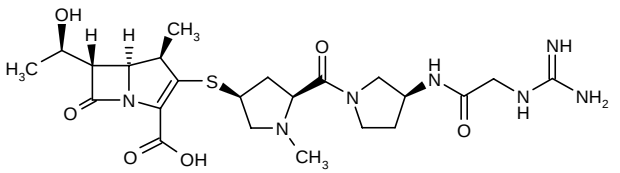
Carbapenem Antibiotic

Prop INN

CS-023
R-1558
Ro-4098463
R-115685 (former code name)

(1*R*,5*S*,6*S*)-2-[5(*S*)-[3(*S*)-(2-Guanidinoacetamido)pyrrolidin-1-ylcarbonyl]-1-methylpyrrolidin-3(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid

InChI=1/C23H35N7O6S/c1-10-17-16(11(2)31)21(34)30(17)18(22(35)36)19(10)37-13-6-14(28(3)9-13)20(33)29-5-4-12(8-29)27-15(32)7-26-23(24)25/h10-14,16-17,31H,4-9H2,1-3H3,(H,27,32)(H,35,36)(H4,24,25,26)/t10-,11-,12+,13+,14+,16-,17-/m1/s1



$C_{23}H_{35}N_7O_6S$
Mol wt: 537.6336

CAS: 222400-20-6

EN: 293388

Abstract

Tomopenem is an injectable carbapenem antibiotic under development for the treatment of common nosocomial infections. The agent shows potent, broad-spectrum activity against both Gram-positive and Gram-negative bacteria, including the clinically important methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*. Tomopenem is stable against human renal dehydropeptidase-I (DHP-I) and has a low rate of renal tubular secretion, endowing it with a relatively extended plasma half-life in comparison to the other commonly used carbapenems imipenem/cilastatin and meropenem. Its potent activity and favorable pharmacokinetic properties are predicted to contribute to clinical efficacy, especially against infections resulting from resistant bacteria and *P. aeruginosa*. Tomopenem is currently in phase II development.

Synthesis

Tomopenem is synthesized as follows:

3(*S*)-Aminopyrrolidine (I) is selectively protected as the 1-Boc derivative (II) by means of Boc_2O in MeOH (1). Subsequent acylation of (II) with chloroacetyl chloride (III) yields the chloroacetamide (IV), which is further converted to the glycinamide (V) upon treatment with ammonium hydroxide in H_2O/MeOH. Condensation of amine (V) with the protected *S*-methylisothiourea (VI) affords the *p*-nitrobenzyloxycarbonyl guanidine (VII), from which the *N*-Boc group is removed under acidic conditions to provide the deprotected pyrrolidine (VIII) (1, 2). Pyrrolidine (VIII) is then acylated with either the mixed anhydride (IX) (1, 2) or with the thiolactone (X) (3) to furnish the 4-acetylthio- (XIa) or the 4-mercaptoprolinamide (XIb), respectively. Coupling of thiol (XIb), optionally generated *in situ* from thioacetate (XIa) and NaOMe, with the carbapenem phosphates (XIIa) or (XIIb) furnishes the protected tomopenem (XIII) (1-4), which is finally deprotected by catalytic hydrogenolysis over Pd/C (1-5). Scheme 1.

The mercatoproline mixed anhydride (IX) can be prepared by two related methods. Reaction of 1-Boc-4(*R*)-hydroxyproline *p*-methoxybenzyl ester (XIV) with methanesulfonyl chloride and DIEA gives the mesylate (XV), which is displaced with thioacetic acid and Cs_2CO_3 in DMAc to yield the acetylsulfanyl derivative (XVI). Acidic Boc group cleavage in (XVI), followed by Eschweiler-Clarke methylation with formaldehyde and formic acid, leads to the *N*-methylproline (XVII), which is converted to the mixed anhydride (IX) by treatment with

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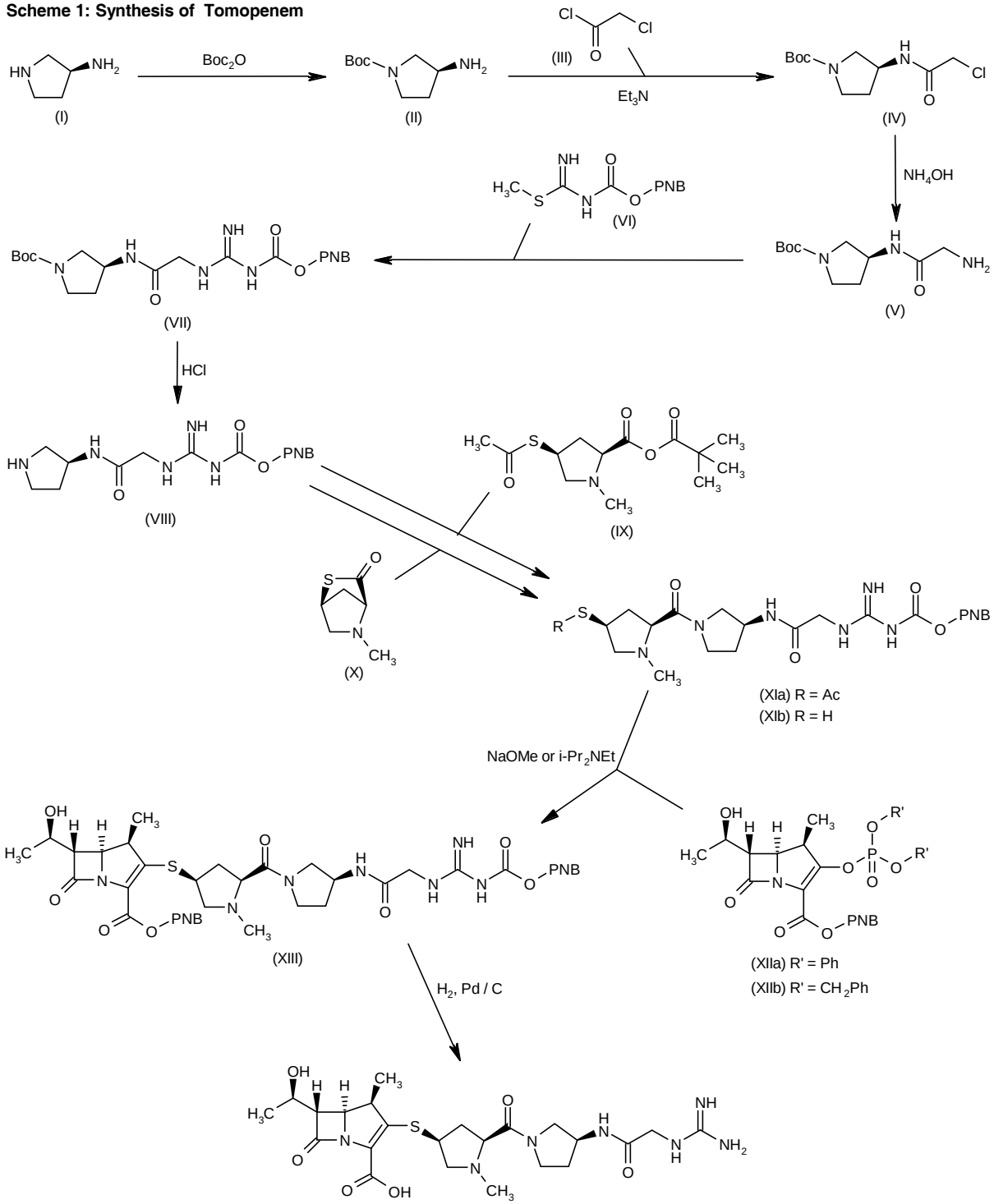
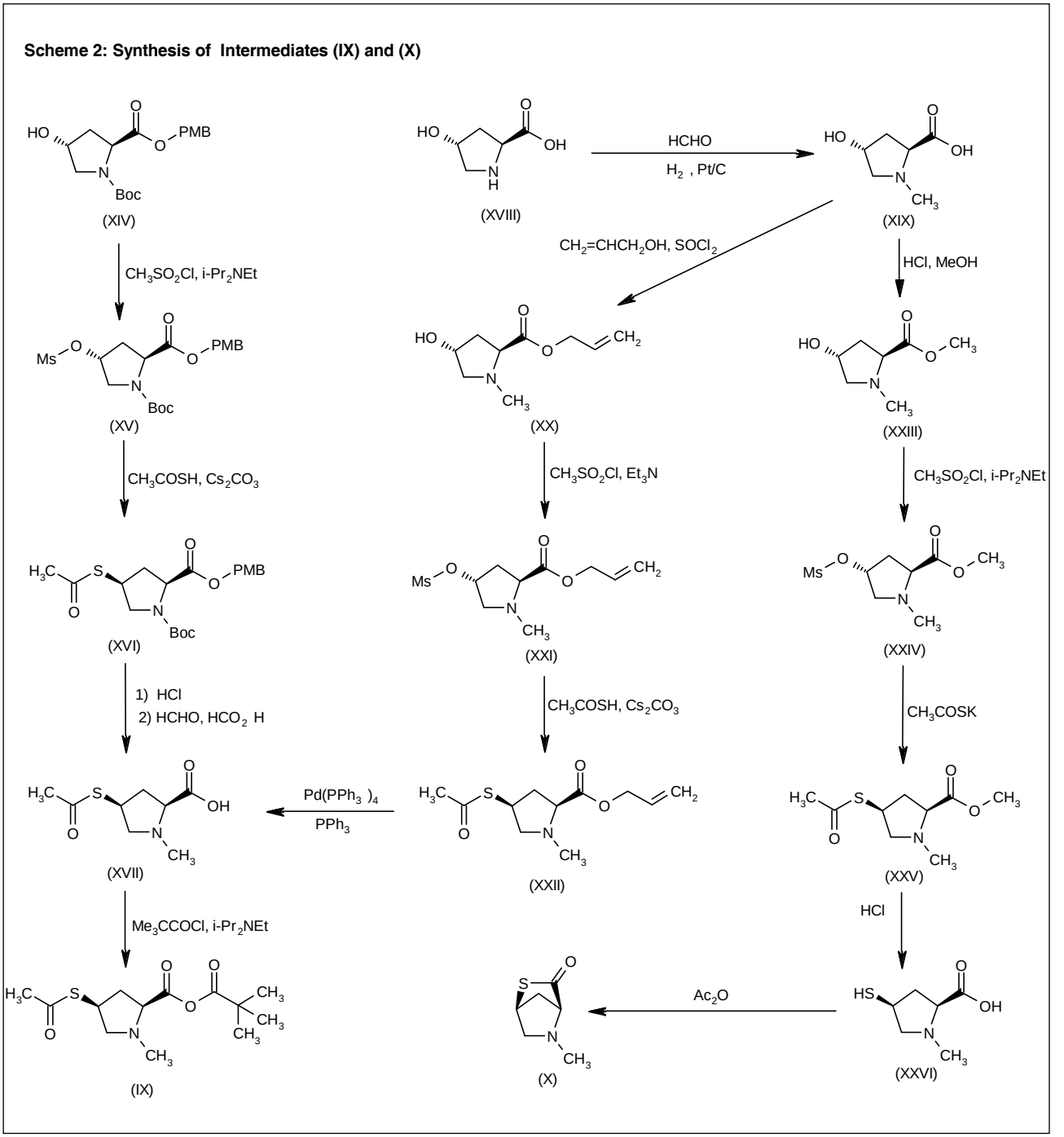
Scheme 1: Synthesis of Tomopenem



pivaloyl chloride and DIEA (2). Alternatively, the reductive methylation of 4(*R*)-hydroxyproline (XVIII) with formaldehyde and H_2 over Pt/C gives 1-methyl-4-hydroxyproline (XIX), which is esterified with allyl alcohol and $SOCl_2$ to give (XX). After conversion of alcohol (XX) to the corresponding mesylate (XXI), displacement with thioacetic acid and Cs_2CO_3 affords the thioacetate (XXII). The allyl ester (XXII) is then selectively removed by means of PPh_3 and $Pd(PPh_3)_4$ to provide the *N*-methylproline (XVII) (1). The thiolactone (X) is obtained by

Scheme 2: Synthesis of Intermediates (IX) and (X)



esterification of 1-methyl-4-hydroxyproline (XIX) with MeOH and HCl, followed by conversion of the resulting hydroxyproline methyl ester (XXIII) to the mesylate (XXIV) with methanesulfonyl chloride and DIEA. After displacement of mesylate (XXIV) with potassium thioacetate in aqueous EtOH, acidic hydrolysis of the obtained thioacetate (XXV) provides 4-mercapto-1-methylproline (XXVI). Subsequent cyclization of (XXVI) in hot acetic anhydride provides the target thiolactone (X) (3). Scheme 2.

Background

The incidence of multidrug-resistant bacterial infections is rising, particularly those acquired in the hospital. The Infectious Disease Society of America (IDSA) estimates that about 2 million people acquire bacterial infections in a U.S. hospital each year, and 90,000 die as a result of their infection. In 2002, approximately 70% of hospital-acquired infections were resistant to at least one commonly used drug. The most common causes of noso-

comial infections in the U.S. include coagulase-negative streptococci, *Staphylococcus aureus* (both methicillin-sensitive [MSSA] and -resistant [MRSA]), *Escherichia coli*, enterococci, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and others, many of which are resistant to at least one commonly used antibiotic, and in some cases many available antibiotics. Thus, there is an urgent need for new antibiotics, particularly those with activity against MRSA and multidrug-resistant *P. aeruginosa* (6-8).

The carbapenems (*e.g.*, imipenem, panipenem, meropenem, biapenem and ertapenem) are highly potent antimicrobial agents belonging to the β-lactam class of antibiotics. They have a broad spectrum of activity against Gram-positive and Gram-negative pathogens, as well as good stability to human renal dehydropeptidase-I (DHP-I). However, available carbapenems are not particularly active against MRSA and increasing resistance has been detected in *P. aeruginosa* (9-11).

Tomopenem (CS-023, R-1558, Ro-4908463, formerly R-115685) is a new parenteral 1-β-methylcarbapenem with a unique guanidine-pyrrolidine side-chain that was designed in an attempt to obtain potent antibacterial activity and improved activity against *P. aeruginosa*. The agent is effective against Gram-positive and Gram-negative pathogens, including MRSA and resistant *P. aeruginosa*, and sufficiently stable to DHP-I (1, 2). It also has an extended plasma half-life relative to the carbapenems imipenem/cilastatin and meropenem.

Preclinical Pharmacology

Tomopenem showed *in vitro* bactericidal activity against clinical isolates with a range of different β-lactam susceptibility phenotypes. Against wild-type *S. aureus*, tomopenem was bactericidal at 1 μg/ml (4 x MIC), and against two resistant strains of *S. aureus* it was bactericidal at 32 μg/ml or less (8 x MIC). Against vancomycin-sensitive- and -resistant *Enterococcus faecalis*, tomopenem was bactericidal at 8 and 4 μg/ml, respectively (4 x MIC) and against both penicillin-sensitive and penicillin-resistant *Streptococcus pneumoniae*, tomopenem was bactericidal at 2 x MIC (0.06 and 1.0 μg/ml, respectively). Tomopenem was also bactericidal against a sensitive strain of *P. aeruginosa* at 2 μg/ml (2 x MIC), against a ceftazidime-resistant strain at 16 μg/ml (8 x MIC) and against a ceftazidime- and imipenem-resistant strain at 8 μg/ml (4 x MIC). The carbapenem displayed bactericidal activity against ceftazidime-sensitive and -resistant *E. coli* at concentrations of 0.06 and 0.12 μg/ml, respectively (2 and 4 x MIC, respectively) (12).

Tomopenem was tested and compared to imipenem, meropenem, ceftazidime, amikacin and levofloxacin against a range of *P. aeruginosa* mutants harboring different resistance mechanisms. Tomopenem was more active than the other carbapenems, ceftazidime and amikacin against all mutants, with MIC values of 0.25-8 μg/ml. Good stability to hydrolysis by most β-lactamases was observed. The antibiotic exerted bactericidal activity against MRSA, penicillin-resistant *S. pneumoniae* and *P. aeruginosa* (13).

Against a panel of Gram-positive and Gram-negative clinical isolates obtained from U.S. hospitals during 2001, the MIC_{90} values for tomopenem ranged from < 0.004 to 4 μg/ml. The strains included staphylococci, streptococci, *H. influenzae, Moraxella catarrhalis* and several isolates of Enterobacteriaceae. Tomopenem had lower activity against *Enterococcus faecium, E. faecalis, Burkholderia cepacia* and *Stenotrophomonas maltophilia* (MIC_{90} > 32 μg/ml). The MIC_{90} against *P. aeruginosa* strains (n=57, including 5 meropenem-resistant isolates) was 8 μg/ml, half that for meropenem (MIC_{90} = 16 μg/ml), one-fourth that for imipenem (MIC_{90} = 32 μg/ml) and considerably lower than that for ceftriaxone and levofloxacin (MIC_{90} > 32 μg/ml). Against the subgroup of meropenem-resistant isolates, tomopenem was 4-8-fold more potent than meropenem. Against oxacillin-resistant coagulase-negative staphylococci (n=39), the MIC_{90} was 4 μg/ml, compared to 16 μg/ml for levofloxacin and meropenem, 32 μg/ml for imipenem and > 32 μg/ml for ceftriaxone, ampicillin and oxacillin (14, 15).

Tomopenem displayed good to excellent *in vitro* activity against Gram-positive clinical isolates, including MRSA, methicillin-resistant *Staphylococcus epidermidis*, penicillin-resistant *S. pneumoniae* and enterococci, with MIC_{90} values in the range 0.25-16 μg/ml, comparable to those of imipenem. Against Gram-negative clinical isolates, including *M. catarrhalis, E. coli, Citrobacter freundii, Morganella morganii* and *P. aeruginosa*, the MIC_{90} values ranged from < 0.032 to 4 μg/ml, comparable to those of meropenem. The combination of tomopenem + vancomycin or amikacin was either synergistic or additive against MRSA and *P. aeruginosa* (16).

The *in vitro* antibacterial activity of tomopenem was further tested against 1,214 clinical isolates covering 32 species obtained from Japanese hospitals over the period 1996-2000. The agent was active against Gram-positive and Gram-negative aerobes and anaerobes, and superior to imipenem, meropenem, ceftriaxone, ampicillin, amikacin and levofloxacin against the following strains: MRSA (n=52; MIC_{90} = 8 μg/ml), methicillin-resistant *S. epidermidis* (n=49; MIC_{90} = 4 μg/ml), penicillin-resistant *S. pneumoniae* (n=47; MIC_{90} = 0.25 μg/ml) and *P. aeruginosa* (n=100, including 21 imipenem-resistant; MIC_{90} = 4 μg/ml; MIC_{90} against the imipenem-resistant subset = 16 μg/ml). Tomopenem also showed excellent activity against a broad spectrum of β-lactamase-producing *E. coli* strains (MIC = 0.016-0.06 μg/ml), comparable to that of meropenem (17).

Tomopenem was also highly active against a panel of European clinical isolates, with MIC_{90} values against MSSA and MRSA (n=60 each) of 0.125 and 8 μg/ml, respectively (compared to 0.03 and > 32 μg/ml, respectively, for imipenem); against penicillin-sensitive and -resistant *S. pneumoniae* (n=60 and 64, respectively), the MIC_{90} values were 0.03 and 0.5 μg/ml, respectively (similar to those for imipenem and meropenem), and against imipenem-sensitive and -resistant *P. aeruginosa* (n=63 and 36, respectively), the respective values were 1 and 4 μg/ml (compared to 2 and 32 and 2 and 16 μg/ml for imipenem and meropenem, respectively) (18).

The *in vitro* activity of tomopenem was examined against sensitive and resistant clinical isolates collected during 2004 from the U.S. and the E.U. For MSSA and MRSA, the MIC_{90} values were 0.25 and 8 μg/ml, respectively, in the U.S. and 0.12 and 16 μg/ml, respectively, in the E.U.; for comparison, the MIC_{90} values for imipenem, meropenem and ertapenem against MRSA from both regions were 32 μg/ml or greater. For coagulase-negative streptococci, the MIC_{90} values were 2 and 4 μg/ml for the U.S. and the E.U., respectively; for penicillin-sensitive and -resistant *S. pneumoniae*, they were 0.008 μg/ml or less and 0.5 μg/ml, respectively, in both regions; for imipenem-sensitive and -resistant *P. aeruginosa*, they were 0.5 and 8 μg/ml, respectively, in the U.S. and 2 and 16 μg/ml, respectively, in the E.U., tomopenem being more potent than ceftazidime or meropenem. The agent was highly potent against expanded-spectrum β-lactam-sensitive and -resistant *E. coli* and *K. pneumoniae* (MIC_{90} < 0.015-0.25 μg/ml), irrespective of the region, with similar activity to other carbapenems (19, 20).

Against a collection of 1,238 clinical isolates obtained from the U.S., Europe and Israel during 2003-2005, the respective MIC_{90} values for tomopenem were as follows: MSSA/MRSA (n=312/333), 0.25/16 μg/ml; methicillin-sensitive/resistant *S. epidermidis* (n=60/52), 0.06/4 μg/ml; *E. faecalis* (n=105), 4 μg/ml; *E. faecium* (n=60), > 32 μg/ml; penicillin-sensitive/resistant *S. pneumoniae* (n=65/42), 0.015/1 μg/ml; *Streptococcus pyogenes* (n=101), 0.015 μg/ml; and *Streptococcus agalactiae* (n=106), 0.06 μg/ml (21).

Tomopenem demonstrated good activity in an *in vitro* screen of 1,438 Gram-negative pathogens collected from hospitals in the U.S. and Europe during 2003-2005, including those with resistance to currently available β-lactams. Against all *P. aeruginosa* (n=212, including 51 ceftazidime-resistant strains and 50 imipenem-resistant strains), the MIC_{90} values were 4 μg/ml for all strains and 8 and 16 μg/ml, respectively, for the resistant strains. Against imipenem-sensitive/resistant *Acinetobacter* spp. (n=91/12), the MIC_{90} values were 16/> 32 μg/ml. Against *H. influenzae* (n=106, including 18 β-lactamase-positive strains), the MIC_{90} was 0.06-0.12 μg/ml. Against a wide range of Enterobacteriaceae (n=1,285, including 130 ceftazidime-resistant strains), the MIC_{90} was 0.12 μg/ml, except against *M. morganii* (n=95), with an MIC_{90} of 1 μg/ml (22).

In vitro assays using *P. aeruginosa* and *S. aureus* revealed a postantibiotic effect (PAE) for tomopenem of approximately 60 min for MSSA and 100-200 min for MRSA. Against imipenem-susceptible *P. aeruginosa*, the PAE was about 70 min, and against imipenem-resistant strains it was 45-80 min. The PAE for tomopenem was generally similar to or greater than that of comparative agents (meropenem, imipenem, vancomycin and ceftazidime) (23).

To identify the rate at which tomopenem-resistant mutants arise, bacteria were cultured overnight on plates containing increasing concentrations of the antibiotic. No mutants were obtained among *S. aureus, S. pneumoniae, E. coli* or *K. pneumoniae*, including β-lactam-resistant variants. Stable mutants were obtained with ceftazidime-resistant, imipenem-sensitive *P. aeruginosa* at a frequency of 3.4×10^{-8}. In these tomopenem-resistant strains, the MIC increased from 2 to 8 μg/ml and was stable after 3 days' passage in drug-free media. Tomopenem-resistant mutants were also obtained from *Enterobacter cloacae*, but they were not stable (24).

The time above MIC (T>MIC) is an important pharmacodynamic parameter for the efficacy of β-lactams. In an *in vitro* model of *S. aureus* bacterial infection, the mean T>MIC for tomopenem giving a 3-log reduction in bacterial count at 24 and 48 h was estimated to be 21% (range = 9.4-43% for 1 MSSA and 5 MRSA strains) and 25.6% (6.6-47.0%), respectively. Using the area under the bacterial kill curve, the mean T>MIC to achieve a 90% maximal response at 0-24-h and 0-48-h intervals was calculated to be 22.8% (range = 1.7-36.2%) and 24.9% (range = 9.0-54.7%), respectively (25).

The antibacterial effect of tomopenem was estimated in an *in vitro* pharmacokinetic model of *S. aureus* infection. Simulating the serum concentrations of tomopenem in a 750 mg t.i.d. i.v. dosing regimen, a > 3.5 log CFU/ml reduction in bacterial counts occurred by 24 h for 1 MSSA and 6 MRSA strains tested. Similar results were obtained using a dosing regimen of 1500 mg t.i.d. and irrespective of the MIC of the strain tested (MIC = 0.06-16 μg/ml). T>MIC was > 70% in all simulatoins (26).

Population pharmacodynamic modeling using the MICs of tomopenem against European and U.S. clinical isolates and pharmacokinetic data from phase I studies were used to estimate the probability of achieving bactericidal exposures (> MIC for > 40% of the dosing interval) against *S. aureus* and *P. aeruginosa*. At exposures obtained with the 1500 mg b.i.d and 750 mg t.i.d. regimens, the drug was estimated to be bactericidal against 96.0% and 96.3% of *S. aureus* and 93.1% and 93.5% of *P. aeruginosa* isolates in the U.S., respectively. The higher dose of 1500 mg t.i.d. was required to provide bactericidal activity against 98.7% of *S. aureus* and 94.0% of *P. aeruginosa* isolates in Europe (27).

Pharmacodynamic modeling was also used to estimate the empiric bactericidal exposure rates of tomopenem against the combined major bacterial causes of nosocomial pneumonia in the U.S. (weighted according to the reported incidence of *S. aureus* [including MRSA], *P. aeruginosa, S. pneumoniae, K. pneumoniae* and *E. coli*). At a dose of 750 mg b.i.d., tomopenem would be expected to be bactericidal against 83.7% of strains, increasing to 96.5% at 1500 mg b.i.d., 96.7% at 750 mg t.i.d. and 99.0% at 1500 mg t.i.d. (28).

In an *in vitro* pharmacodynamic model simulating the conditions of a 350 mg b.i.d. dose in humans, tomopenem caused a maximal decrease in *P. aeruginosa* of 3.56 $\log_{10}$ CFU/ml or more, with a final reduction of 0.03 $\log_{10}$ CFU/ml and an area under the killing curve of 27.8 $\log_{10}$ CFU/ml x h. Similar bactericidal activities were achieved for meropenem and imipenem at the simulated dosing regimen of 500 mg t.i.d. In a neutropenic mouse model of

thigh muscle infection, tomopenem suppressed the growth of *P. aeruginosa* at doses equivalent to 350 mg or above in humans and equivalent to 125 mg or above in normal mice (29).

Another *in vitro* pharmacodynamic model of MRSA infection using doses simulating a human regimen of 350 mg b.i.d. tomopenem showed a maximal decrease in MRSA of 3.25 $\log_{10}$ CFU/ml or more, with a final reduction of 0.68 $\log_{10}$ CFU/ml and an area under the killing curve of 37.5 $\log_{10}$ CFU/ml x h. Respective values for meropenem at the simulated dosing regimen of 500 mg t.i.d. were 2.55 $\log_{10}$ CFU/ml, 0.50 $\log_{10}$ CFU/ml and 73.0 $\log_{10}$ CFU/ml x h, and for imipenem they were 1.90 $\log_{10}$ CFU/ml, 0.84 $\log_{10}$ CFU/ml and 8.70 $\log_{10}$ CFU/ml x h. In a mouse model of sepsis caused by MRSA, > 80% survival was achieved in immunocompetent and neutropenic mice at doses equivalent to 500 mg or more in humans (30, 31).

Using mouse models of systemic infection (urinary and respiratory tract infections), tomopenem was effective against all strains tested, including penicillin-resistant *S. pneumoniae* (ED_{50} = 0.55 mg/kg s.c.), MRSA (ED_{50} = 7.9 mg/kg s.c.) and *P. aeruginosa* (ED_{50} = 0.95 mg/kg s.c.). These values were comparable to those for imipenem/cilastatin and superior to those for meropenem, ceftriaxone and ceftazidime in the same models. In murine models of pneumonia caused by penicillin-resistant *S. pneumoniae*, significant reductions in viable counts were seen at 2 and 10 mg/kg tomopenem (17, 32).

In mouse models of systemic infection caused by MRSA or *P. aeruginosa*, the ED_{90} could be achieved when the plasma concentration of tomopenem remained above the MIC for < 20% of the dosing interval. Extrapolating from this figure, a 700 mg b.i.d. dose in humans would be expected to achieve plasma levels of 13 μg/ml for 20% of the dosing interval, therefore covering most clinical isolates of MRSA or *P. aeruginosa* at this dose (33).

Pharmacokinetics and Metabolism

In the presence of DHP-I in human kidney homogenates, tomopenem exhibited a comparable rate of hydrolysis to meropenem and a lower rate compared to imipenem, suggesting the possibility of dosing without cilastatin (a DHP inhibitor) (1, 2).

Following s.c. injection in mice, the urinary recovery of tomopenem (50 mg/kg) was 52.8% (0-24 h) compared to 29.2% for meropenem at the same dose (1).

After a single s.c. injection of 20 mg/kg in mice, a C_{max} of 20 μg/ml was reached at 0.25 h; plasma levels of tomopenem were higher than those for meropenem and similar to imipenem/cilastatin. The half-life was 0.18 h, similar to that for imipenem/cilastatin (0.14 h) and meropenem (0.10 h) (17).

The renal handling of tomopenem was explored in male Japanese White rabbits. Following i.v. infusion of tomopenem (2 mg/kg + 0.121 mg/min), the renal clearance/glomerular filtration rate ratio was 1. This ratio was not affected by co-administration of probenecid, an agent known to reduce the renal tubular secretion of some drugs. By comparison, the renal clearance/glomerular filtration rate following meropenem (5 mg/kg + 0.3 mg/min) infusion was 3, which was reduced to about 1 upon co-administration with probenecid. The ratio of tomopenem in the renal cortex/plasma was 0.6, while that for meropenem was 3, decreasing to 0.6 upon co-administration with probenecid. Cells expressing the human organic anion transporters hOAT1 and hOAT3 took up meropenem, but not tomopenem. These data suggest that the rate of renal tubular secretion of tomopenem via organic anion transporters is relatively low compared to that of meropenem, which may possibly explain the longer plasma half-life of tomopenem in man (approximately 2 h) compared to the latter (approximately 1 h) (34, 35).

Using [^{14}C]-labeled tomopenem, the distribution, metabolism and excretion were studied in rats, dogs and monkeys. Whole-body autoradioluminograms of rats showed distribution of the agent throughout the body, except for the central nervous system and testes. In rat plasma, the primary metabolite of tomopenem (R-131624, with an open β-lactam ring and pharmacologically inactive) became the dominant metabolite within 30 min of administration; only low levels of R-131624 were detected in the plasma of dogs and monkeys. Tomopenem was concentrated in the kidneys, the site of its excretion, and around 80-90% of the radioactive material administered was recovered in the urine of all species. In rat urine, tomopenem accounted for 30% of the dose and R-131624 for another 30%, while in monkey urine, tomopenem accounted for approximately 50% of the dose and R-131624 for 20%. In rats, dogs and monkeys, the plasma half-life of tomopenem was 0.16, 0.75 and 1.4 h, respectively. The $AUC_{0-\infty}$ at 10 mg/kg was 10.2, 18.8 and 103.9 μg.h/ml in rats, dogs and monkeys, respectively, and the total clearance was 16.9, 4.19 and 1.62 ml/min/kg, respectively. The steady-state volume of distribution was comparable among the different animals (172-259 ml/kg), as was protein binding (5-15.6%) (36, 37). Using these and additional data from mice and rabbits, a pharmacokinetic model was built to predict the disposition of tomopenem (simulated dose of 700 mg by 30-min i.v. infusion) in humans. The $t_{1/2}$ in man was predicted to be > 2 h, longer than for imipenem/cilastatin or meropenem. Total plasma clearance, however, was significantly underestimated due to inclusion of data from monkeys. It was suggested that net renal clearance in monkeys may be predominantly due to tubular reabsorption, which is not the case in the other animals, and probably not in humans. Excluding the monkey data, the clearance value was calculated to be 138 ml/min, much closer to the actual mean value of 137 ml/min, and the volume of distribution was 19.5 l (actual mean value from phase I studies = 17.4 l). This allowed a plasma concentration-time profile to be modeled that was in good agreement with the profile observed in humans (38).

In a double-blind, placebo-controlled pharmacokinetic and safety study, 56 healthy Caucasian male volun-

teers were administered tomopenem (50, 100, 200, 350, 700, 1400 and 2100 mg) or placebo (6 active and 2 placebo per dose group) as a 30-min i.v. infusion. The active agent was well tolerated and there were no serious adverse events or changes in clinically important measures such as ECG, vital signs or laboratory tests. The C_{max} and AUC increased proportionally with the dose, and the clearance and steady-state volume of distribution remained constant over the dose range, suggesting linear pharmacokinetics. The elimination half-life (1.47-2.04 h) was greater than that reported for imipenem/cilastatin and meropenem (< 1 h). The cumulative urinary excretion rate reached 51.6-74.1% of the dose within 24 h of administration, and the mean renal clearance was 4.87 l/h. It was suggested that a relatively low rate of tubular secretion may contribute to the extended half-life of the agent (39, 40).

In another similar study, 60 healthy Japanese male volunteers were administered tomopenem (100, 200, 375, 750, 1500 and 2100 mg) or placebo (8 active and 2 placebo per dose group) as a 30-min i.v. infusion. The active agent was well tolerated, and there were no serious adverse events or changes in ECG, vital signs or laboratory tests. The increase in C_{max} and AUC was linear and proportional to dose, and the elimination half-life was 1.51-1.86 h. The cumulative urinary recovery within 24 h of administration was 63.9-73% for the parent compound and 13.6-16% for its major metabolite (41).

Safety

The safety of tomopenem was studied in rats and rabbits. In a single-dose toxicity study, tomopenem was not lethal up to 2 g/kg i.v. in rats. After 4 days of repeated dosing, no toxicity was observed in rats even at 1 g/kg. After a single i.v. infusion of 200 mg/kg in rabbits, there were no signs of nephrotoxicity. In neurotoxicity studies, sharp waves in spontaneous electroencephalogram (EEG) were observed in 1 of 5 rats after single i.v. doses of 100 or 200 μg tomopenem; this compares favorably with cefazolin and imipenem, which evoked seizure discharge in 2 of 5 rats at 50 and 10 μg, respectively (42).

Sources

Daiichi Sankyo Co., Ltd. (JP); licensed to F. Hoffmann-La Roche, Ltd. (CH).

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