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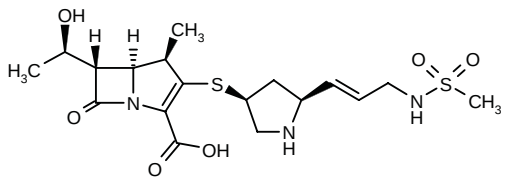
# DA-1131

*Carbapenem Antibiotic*

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-[5(*S*)-[3-(methanesulfonamido)-1(*E*)-propenyl]pyrrolidin-3(*S*)-ylsulfanyl]-1-methyl-1-carba-2-penem-3-carboxylic acid



$C_{18}H_{27}N_3O_6S_2$ Mol wt: 445.5583

CAS: 169285-98-7

EN: 235904

## Synthesis

The pyrrolidine derivative (VIII), which was synthesized from hydroxy proline (I) through 12 steps (1), was coupled with the enolphosphate intermediate (XI) (2) available from acetoxyazetidinone (IX) (3). Deprotection of the DA-1131 ester (XII) was performed with Pd(II) and tin hydride reagents (2, 3). After work-up, the resulting excess $H_2O$ was freeze-dried to afford the crude yellowish solid which was further recrystallized in $H_2O$/acetone to give pure DA-1131 (3). Scheme 1.

## Description

Light yellowish powder.

## Introduction

DA-1131, a new anionic carbapenem antibiotic, has a broad spectrum of activity against both Gram-positive and Gram-negative organisms (4). The antibacterial activity of DA-1131 was comparable or slightly superior to those of imipenem-cilastatin and meropenem against both Gram-positive and Gram-negative organisms. In particular, DA-1131 was more active than other carbapenems against *Pseudomonas aeruginosa* (4). DA-1131 was resistant to degradation by various types of β-lactamases (5) and was relatively stable against hydrolysis by ICR mouse, Sprague-Dawley rat, New Zealand white rabbit, beagle dog and human renal dehydropeptidase I (DHP-I) compared with imipenem and meropenem (6). Judging from the maximum velocity-to-Michaelis-Menten constant ($V_{max}/K_m$) ratios, DA-1131 showed relatively greater resistance to mouse, rat, rabbit, dog and human renal DHP-I than imipenem or meropenem; the ratios of DA-1131 for resistance to DHP-1 were from 1.3-4.6 times higher than those of imipenem and meropenem. DA-1131 is now being evaluated in a preclinical study.

Earlier publications from our laboratories reported on various aspects of DA-1131, including high-performance liquid chromatographic (HPLC) analysis in biological fluids (7, 8); stability, tissue metabolism, tissue distribution and blood partition between plasma and blood cells (9); pharmacokinetics in mice, rats, rabbits and dogs (10); interspecies pharmacokinetics scaling (11); pharmacokinetics in special animal populations such as rats with uranyl nitrate-induced acute renal failure (12), rats with alloxan-induced diabetes mellitus (13), rabbits with endotoxin-induced pyrexia (14), spontaneously hypertensive rats and deoxycorticosterone acetate-salt-induced hypertensive rats (15) and rats treated with cilastatin (16); effect of probenecid on the renal excretion mechanism of DA-1131 in rats, rabbits (17) and dogs (18); and nephroprotective effect of betamipron in rabbits (19).

DA-1131 was unstable when incubated in a water-bath shaker kept at 37 °C and at a rate of 50 oscillations per min in various pH solutions, especially at low and high pHs at a drug concentration of 10 μg/ml; the first-order degradation half-lives of DA-1131 were 0.260, 1.23, 2.20, 7.16, 14.2, 10.5, 31.3, 21.3, 0.262, 0.241 and 1.45 h for pH solutions of 1-11, respectively (9). DA-1131 was also unstable after incubation in 5 human gastric juices (pHs of 2.90, 6.98, 2.27, 6.93 and 1.21), whereas it appeared

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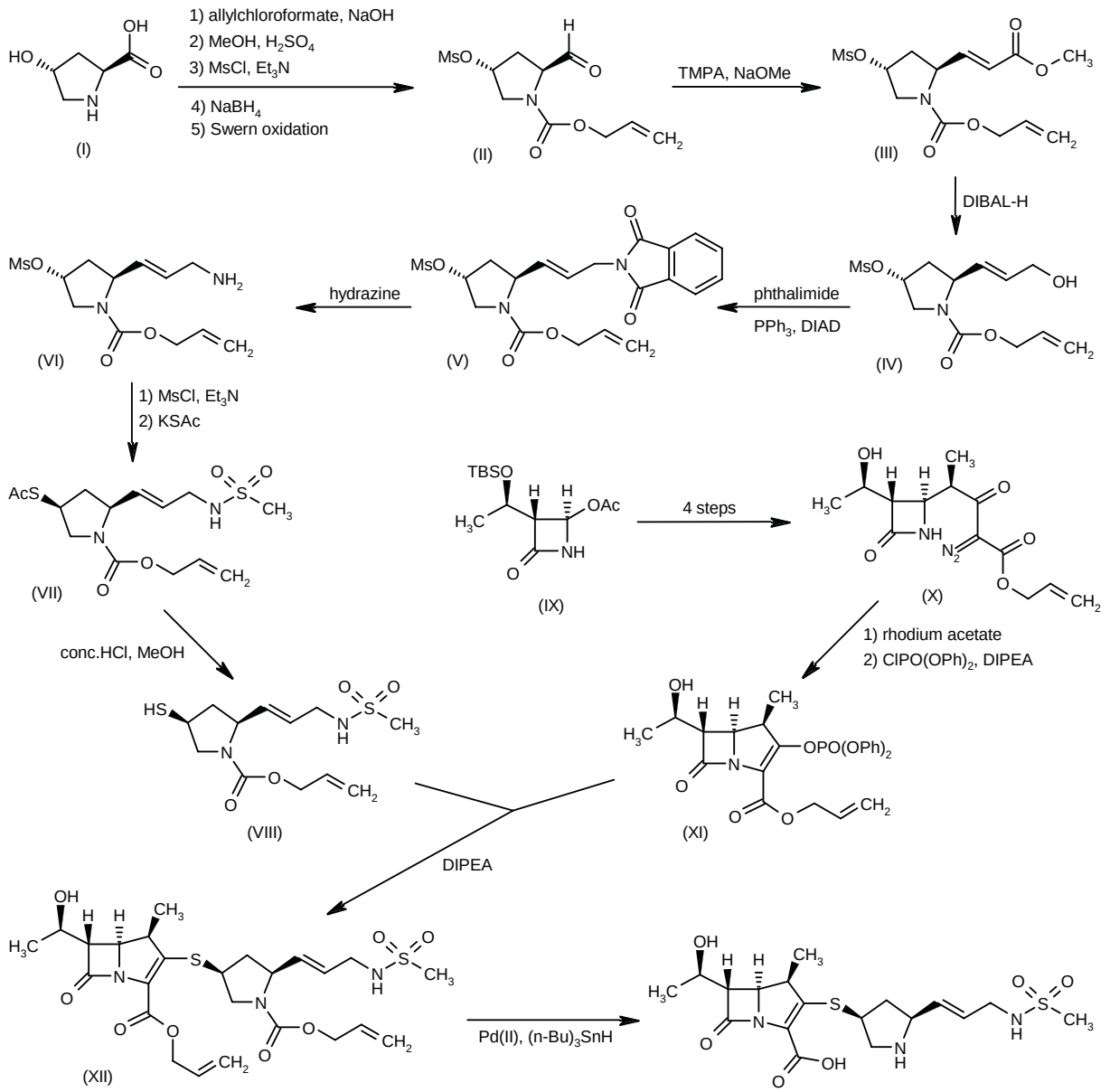
**Scheme 1: Synthesis of DA-1131**




to be stable in human plasma for up to 12 h storage at –20 °C (9). Although whole blood and plasma concentrations decreased with increasing incubation time, the plasma-to-blood cell concentration ratios of DA-1131 were independent of its blood concentrations when rabbit whole blood was incubated for up to 2 h; the mean values were 5.56 ± 1.47, 5.80 ± 2.19 and 4.61 ± 1.82 at drug blood concentrations of 2, 10 and 20 μg/ml, respectively, in 3 rabbits (9). There was also considerable "blood storage effect" (the change in plasma concentration of drug due to the time elapsed between collection and centrifugation of the blood sample) in the plasma concentration of DA-1131 in rabbits (9); therefore, blood samples should be centrifuged immediately as soon as they are collected. The plasma protein binding of DA-1131 in rats, rabbits and dogs was less than 10% at drug plasma concentrations ranging from 10-500 μg/ml using an ultrafiltration method (10).

## Antimicrobial Activity

The *in vitro* activity of DA-1131 was confirmed by susceptibility testing using an agar dilution method

*Table I: Antibacterial activity of DA-1131 and reference antibiotics against Gram-positive clinical isolates.*

| Organism | Drug | MIC range (μg/ml) | $MIC_{50}$ (μg/ml) | $MIC_{90}$ (μg/ml) |
|---|---|---|---|---|
| *S. aureus* (MSSA, 20) | DA-1131 | 0.025 - 0.05 | 0.025 | 0.05 |
| | IPM/CS | 0.025 | 0.025 | 0.025 |
| | MEPM | 0.1 - 0.2 | 0.2 | 0.2 |
| *S. aureus* (MRSA, 18) | DA-1131 | 6.25 - 25 | 12.5 | 25 |
| | IPM/CS | 6.25 - 100 | 50 | 100 |
| | MEPM | 12.5 - 50 | 50 | 50 |
| *S. epidermidis* (32) | DA-1131 | 0.025 - 0.2 | 0.05 | 0.1 |
| | IPM/CS | 0.025 - 0.05 | 0.025 | 0.05 |
| | MEPM | 0.05 - 0.39 | 0.1 | 0.2 |
| *S. pyogenes* (27) | DA-1131 | ≤ 0.025 | ≤ 0.025 | ≤ 0.025 |
| | IPM/CS | ≤ 0.025 | ≤ 0.025 | ≤ 0.025 |
| | MEPM | ≤ 0.025 | ≤ 0.025 | ≤ 0.025 |
| *S. pneumoniae* (30) | DA-1131 | ≤ 0.025 | ≤ 0.025 | ≤ 0.025 |
| | IPM/CS | ≤ 0.025 | ≤ 0.025 | ≤ 0.025 |
| | MEPM | ≤ 0.025 - 0.1 | ≤ 0.025 | ≤ 0.025 |
| *E. faecalis* (20) | DA-1131 | 3.13 - 6.25 | 3.13 | 6.25 |
| | IPM/CS | 0.78 - 1.56 | 1.56 | 1.56 |
| | MEPM | 6.25 - 12.5 | 6.25 | 12.5 |

MSSA: methicillin susceptible *S. aureus*; MRSA: methicillin resistant *S. aureus*; IMP/CS: imipenem-cilastatin; MEPM: meropenem.

recommended by the Japan Society of Chemotherapy. DA-1131 inhibited methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Enterrococcus faecalis* at respective $MIC_{90}$ values of 0.05, ≤ 0.025, ≤ 0.025 and 6.25 μg/ml (Table I). The $MIC_{90}$ values of DA-1131 for *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Entero-bacter cloacae*, *Serratia marcescens*, *Branhamella catarrhalis*, *Neisseria gonorrhoeae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii* and *Haemophilus influenzae* were 0.05-0.78 μg/ml. DA-1131 was 2- to 4-fold more active than imipenem and meropenem against *Pseudomonas aeruginosa*, with $MIC_{50}$ and $MIC_{90}$ values of 0.2 and 1.56 μg/ml, respectively (Table II). DA-1131 showed a well-balanced and potent antibacterial spectrum against both Gram-positive and Gram-negative bacteria, in particular against *Pseudomonas aeruginosa*. In addition, DA-1131 inhibited ceftazidime-resistant Gram-negative bacteria, including broad spectrum β-lactamase producing isolates. The MBC values of DA-1131 were similar to the MIC values against various bacterial species tested.

The potent *in vitro* activity of DA-1131 against a wide range of bacteria was confirmed in lethal systemic infection models. DA-1131 was highly efficacious against systemic infections in mice due to *S. aureus*, *K. pneumoniae*, *E. cloacae*, *P. mirabilis* and *P. aeruginosa*, as well as lethal systemic neutropenia in mice due to *P. aeruginosa*. DA-1131 also demonstrated potent therapeutic effects in local infections such as pneumonia due to *K. pneumo-niae* and ascending pyelonephritis due to *P. mirabilis*.

**Pharmacokinetics**

After intravenous administration of DA-1131 to mice (20, 50, 100 and 200 mg/kg), rats (50, 100, 200 and 500 mg/kg), rabbits (20, 50, 100 and 200 mg/kg) and dogs (10, 20, 50, 100 and 200 mg/kg), the pharmacokinetic parameters were independent of dose ranges studied in all four animal species (10). However, after i.v. administration, renal clearance was significantly slower and amount of DA-1131 excreted in 24-h urine as unchanged drug decreased significantly in rabbits (at 200 mg/kg) and dogs (at 100 and 200 mg/kg) due to drug-induced impaired kidney function (10).

In order to reduce the nephrotoxicity of DA-1131 in rabbits, betamipron (200 mg/kg i.v.) was coadministered with the 200 mg/kg dose of DA-1131. Extensive tubular necrosis was observed without betamipron but was not observed with betamipron 8 h after i.v. administration of DA-1131 as shown on kidney microscopy (19). In rabbits treated with betamipron, the amounts and tissue-to-plasma ratios of DA-1131 in renal cortex and whole kidney decreased significantly (65-91% decrease) at both 30 min and 2 h after DA-1131 administration, indicating that the accumulation of DA-1131 in rabbit renal cortex and whole kidney was inhibited by betamipron (19).

The total body and renal clearances and apparent volume of distribution at steady state of DA-1131 based on the above animal data at 50 mg/kg were analyzed as a function of species body weight using the allometric equation for interspecies scaling, and were used to predict these parameters in humans. Significant linear relationships were obtained between log of the above men-

*Table II: Antibacterial activity of DA-1131 and reference antibiotics against Gram-negative clinical isolates.*

| Organism | Drug | MIC range (μg/ml) | $MIC_{50}$ (μg/ml) | $MIC_{90}$ (μg/ml) |
|---|---|---|---|---|
| *E. coli* (19) | DA-1131 | 0.025 - 0.05 | 0.05 | 0.05 |
| | IPM/CS | 0.1 - 0.2 | 0.2 | 0.2 |
| | MEPM | 0.025 | 0.025 | 0.025 |
| *K. pneumoniae* (17) | DA-1131 | 0.05 - 0.2 | 0.05 | 0.1 |
| | IPM/CS | 0.1 - 0.39 | 0.2 | 0.39 |
| | MEPM | 0.025 - 0.2 | 0.05 | 0.05 |
| *C. freundii* (15) | DA-1131 | 0.05 - 0.1 | 0.05 | 0.05 |
| | IPM/CS | 0.2 - 0.78 | 0.39 | 0.78 |
| | MEPM | 0.025 - 0.05 | 0.025 | 0.05 |
| *E. aerogenes* (10) | DA-1131 | 0.05 - 0.1 | 0.05 | 0.1 |
| | IPM/CS | 0.39 - 1.56 | 0.78 | 1.56 |
| | MEPM | 0.025 - 0.1 | 0.05 | 0.1 |
| *E. cloacae* (23) | DA-1131 | 0.025 - 0.2 | 0.05 | 0.2 |
| | IPM/CS | 0.1 - 0.78 | 0.39 | 0.78 |
| | MEPM | 0.025 - 0.2 | 0.05 | 0.1 |
| *S. marcescens* (21) | DA-1131 | 0.1 - 0.39 | 0.1 | 0.2 |
| | IPM/CS | 0.39 - 3.13 | 0.39 | 0.78 |
| | MEPM | 0.05 - 0.2 | 0.05 | 0.1 |
| *P. mirabilis* (7) | DA-1131 | 0.05 - 0.39 | 0.2 | 0.39 |
| | IPM/CS | 0.39 - 6.25 | 1.56 | 3.13 |
| | MEPM | 0.05 - 0.2 | 0.1 | 0.1 |
| *P. vulgaris* (39) | DA-1131 | 0.05 - 1.56 | 0.39 | 0.78 |
| | IPM/CS | 0.78 - 6.25 | 3.13 | 3.13 |
| | MEPM | 0.1 - 0.39 | 0.2 | 0.2 |
| *P. stuartii* (18) | DA-1131 | 0.025 - 0.39 | 0.2 | 0.39 |
| | IPM/CS | 0.2 - 3.13 | 1.56 | 1.56 |
| | MEPM | 0.025 - 0.39 | 0.025 | 0.05 |
| *M. morganii* (20) | DA-1131 | 0.1 - 0.39 | 0.2 | 0.39 |
| | IPM/CS | 1.56 - 3.13 | 3.13 | 3.13 |
| | MEPM | 0.05 - 0.2 | 0.1 | 0.1 |
| *B. catarrhalis* (32) | DA-1131 | ≤ 0.025 | ≤ 0.025 | ≤ 0.025 |
| | IPM/CS | ≤ 0.025 - 0.1 | 0.05 | 0.1 |
| | MEPM | ≤ 0.025 | ≤ 0.025 | ≤ 0.025 |
| *N. gonorrhoeae* (15) | DA-1131 | ≤ 0.025 - 0.05 | ≤ 0.025 | 0.05 |
| | IPM/CS | 0.05 - 0.2 | 0.1 | 0.1 |
| | MEPM | ≤ 0.025 - 0.05 | ≤ 0.025 | ≤ 0.025 |
| *H. influenzae* (28) | DA-1131 | 0.1 - 0.78 | 0.2 | 0.39 |
| | IPM/CS | 0.39 - 3.13 | 1.56 | 3.13 |
| | MEPM | ≤ 0.025 - 0.1 | 0.05 | 0.1 |
| *P. aeruginosa* (17) | DA-1131 | 0.05 - 1.56 | 0.2 | 1.56 |
| | IPM/CS | 0.39 - 3.13 | 0.78 | 3.13 |
| | MEPM | 0.2 - 3.13 | 0.78 | 3.13 |

IPM/CS: imipenem-cilastatin; MEPM: meropenem.

tioned parameters and log body weight. The DA-1131 data obtained from laboratory animals was used to generate preliminary estimates of the drug's pharmacokinetic parameters in humans (11).

Active renal secretion of DA-1131 was observed in rabbits and in rats, while renal reabsorption of the drug was observed in dogs (10). Similar results were found in studies with probenecid, an anion transport inhibitor. The effects of probenecid on the renal excretion of DA-1131were investigated after a 1-min i.v. infusion of DA-1131 to rabbits (100 mg/kg), rats (50 mg/kg) and dogs (10 mg/kg) with or without 50 mg/kg of probenecid (17, 18). The renal clearance of DA-1131 was significantly slower in probenecid-treated rabbits compared to non-treated controls, and in rats values were comparable between treated and nontreated animals (17). In dogs, however, renal clearance was not significantly affected by treatment with probenecid, suggesting that the tubular reabsorption of DA-1131 was not inhibited by probenecid (18).

Since the structure of DA-1131 resembles a dipeptide, DA-1131 is metabolized by renal DHP-I, located on the

brush border of the proximal tubular cell (16). Species differences with regard to the effects of cilastatin (a DHP-I inhibitor) on the pharmacokinetics of DA-1131 were observed after administration of DA-1131 with or without cilastatin to rats, rabbits and dogs (16). After a 1-min i.v. infusion of DA-1131, the nonrenal clearance of the drug was significantly slower in rats and rabbits when the carbapenem was coadministered with cilastatin; renal metabolism of DA-1131 by rat and rabbit renal DHP-I was inhibited by cilastatin (16). However, coadministration with cilastatin to dogs did not affect the nonrenal clearance of DA-1131 (16).

The pharmacokinetics of DA-1131 were also investigated in several disease models in rats. In rats with hypertension, the nonrenal clearance of DA-1131 (50 mg/kg i.v.) was significantly faster in 6- and 16-week-old spontaneously hypertensive rats (SHRs) than in their respective control Kyoto-Wistar rats (15). However, opposite results were obtained from 16-week-old deoxycorticosterone acetate-salt-induced hypertensive rats (15). The significantly faster nonrenal clearance of DA-1131 in 16-week-old SHRs was due to hereditary characteristics rather than the hypertensive state itself (15). In rats with acute renal failure induced by uranyl nitrate, the renal clearance (because of a significant decrease in the 8-h urinary excretion of unchanged DA-1131 due to impaired kidney function) and nonrenal clearance (because of a significant decrease in the metabolism of DA-1131 in the kidney) were significantly slower than those in control rats (12). In rats with water deprivation for 72-h, the renal clearance (because of a significant decrease in 8-h urinary excretion of unchanged DA-1131 due to impaired kidney function) and nonrenal clearance (because of a significant decrease in the metabolism of DA-1131 in the kidney, as shown by the significant decrease in total renal DHP-I enzyme activity) were significantly slower than those in control rats (21). In rats with alloxan-induced diabetes mellitus, the renal clearance (because of considerably decreased glomerular filtration rate of DA-1131) and nonrenal clearance (possibly because of the considerably slower metabolism in rat liver and kidney) were significantly slower than those in control rats (13). Finally, in lipopolysaccharide-induced febrile rabbits (LPSIF), compensatory changes in renal and nonrenal clearances of DA-1131 were observed (14). For example, nonrenal clearance was significantly slower and renal clearance was significantly faster than in control rabbits. Pharmacokinetic studies on metabolites of DA-1131 were not performed.

## Toxicity

The acute toxicity of intravenously administered DA-1131 was studied in mice and rats. DA-1131 was well tolerated in these species up to a dose of 3000 mg/kg. Clinical signs associated with this dose consisted of piloerection, increased respiratory rates, partially closed eyelids, temporary lethargy and tonic convulsion. The highest nonlethal i.v. dose of DA-1131 in mice and rats was considered to be 3000 mg/kg in both species. A 2-week i.v. dose-finding study of DA-1131 was also conducted in rats. At the high dose of 2000 mg/kg, the animals showed enlargement of cecum and mild biochemical changes. No signs of nephrotoxicity were observed after single and repeated i.v. administration of DA-1131 in rodents. In rabbits, however, a single i.v. dose of DA-1131 at 100 mg/kg or above induced tubular degeneration and focal necrosis accompanied by dose-related elevation of blood urea and creatinine levels. Repeated i.v. doses of DA-1131 for 7 days in cynomolgus monkeys induced clear signs of nephrotoxicity both clinically and histopathologically at 500 mg/kg/day, whereas the same dose of meropenem did not induce any signs of nephrotoxicity. However, no renal changes were seen in monkeys receiving DA-1131 at 500 mg/kg/day and concomitant dose of benzoyltaurine, a nephroprotectant, at 500 mg/kg/day or above. As mentioned earlier, renal toxicity of DA-1131 was attenuated or disappeared by administration of betamipron in rabbits (19).

DA-1131 was not antigenic in acute systemic anaphylaxis and passive cutaneous anaphylaxis studies in guinea pigs. In addition, DA-1131 did not show clastogenic potential in the rodent micronucleus test. Neurotoxic potential of DA-1131 was evaluated using pentylenetetrazole-induced convulsion model in mice. Intravenous administration of imipenem (400 mg/kg) to pentylenetetrazole-pretreated mice induced severe tonic convulsion and death. However, DA-1131 did not show proconvulsive potential up to the highest dose of 800 mg/kg. DA-1131 showed less inhibition on γ-aminobutyric acid receptor than imipenem and meropenem.

## Manufacturer

Dong-A Pharmaceutical Co., Ltd. (KR).

## References

1. Rhee, J.K., Lee, C.W., Im, W.B., Lim, J.I., Cho, J.H., Choi, S.H. *Synthetic study of met-SH (hydroxy proline derivative), side chain of DA-1131.* Korean J Med Chem 1988, 8: 2-5.

2. Rhee, J.K., Lee, C.W., Im, W.B., Lim, J.I., Cho, J.H., Choi, S.H. *Synthesis of some carbapenem derivatives and their antibacterial activity.* Korean J Med Chem 1993, 3: 72-75.

3. Chang, M.S., Rhee, J.K., Lee, C.W., Im, W.B., Lim, J.I., Cho, J.H., Choi, S.H. (Dong-A Pharmaceutical Co., Ltd.). *Synthesis of new carbapenem derivatives.* WO 9514692.

4. Kim, G.W., Chang, M.S., Lee, C.W., Chong, Y.S., Yang, J. *Comparative in vitro antibacterial activity of DA-1131, a new carbapenem antibiotic (I).* Annu Meet Korea Soc Appl Pharmacol (Nov 8, Seoul) 1996, Abst p 232.

5. Choi, S.H., Kim, G.W., Kim, J.Y., Lim, G.J., Chung, D.Y., Kim, W.B., Yang, J. *Interaction of DA-1131, a new carbapenem antibiotic, with bacterial β-lactamases.* Annu Meet Korea Soc Appl Pharmacol (Nov 8, Seoul) 1996, Abst p 237.

6. Kim, J.Y., Kim, G.W., Choi, S.H., We, J.S., Park, H.S., Yang, J. *Renal dehydropeptidase-I (DHP-I) stability and pharmacokinetics of DA-1131, a new carbapenem antibiotic.* Annu Meet Korea Soc Appl Pharmacol (Nov 8, Seoul) 1996, Abst p 238.

7. Kim, S.H., Kwon, J.W., Yang, J., Lee, M.G. *Determination of a new carbapenem derivative, DA-1131, in plasma and urine by high-performance liquid chromatography.* J Chromatogr B 1997, 688: 95-99.

8. Lee, E.D., Lee, S.D., Kim, W.G., Yang, J., Kim S.H., Lee, M.G. *Determination of a new carbapenem antibiotic, DA-1131, in rat plasma, urine, and bile by column-switching high-performance liquid chromatography.* Res Commun Mol Pathol Pharmacol 1996, 94: 171-9.

9. Kim, S.H., Kim, W.B., Lee, M.G. *Stability, tissue metabolism, tissue distribution, and blood partition of DA-1131, a new carbapenem.* Res Commun Mol Pathol Pharmacol 1995, 90: 347-62.

10. Kim, S.H., Kwon, J.W., Lee, M.G. *Pharmacokinetics and tissue distribution of a new carbapenem, DA-1131, after intravenous administration to mice, rats, rabbits, and dogs.* Biopharm Drug Dispos 1998, 19: 219-29.

11. Kim, S.H., Kim, W.B., Lee, M.G. *Interspecies pharmacokinetic scaling of a new carbapenem, DA-1131, in mice, rats, rabbits, and dogs, and prediction of human pharmacokinetics.* Biopharam Drug Dispos 1998, 19: 231-5.

12. Kim, S.H., Shim, H.J., Kim, W.B., Lee, M.G. *Pharmacokinetics of a new carbapenem, DA-1131, after intravenous administration to rats with uranyl nitrate-induced acute renal failure.* Antimicrob Agents Chemother 1998, 42: 1217-21.

13. Kim, S.H., Kim, W.B., Lee, M.G. *Pharmacokinetics of a new carbapenem, DA-1131, after intravenous administration to rats with alloxan-induced diabetes mellitus.* Biopharm Drug Dispos 1998, 19: 303-8.

14. Kim, S.H., Kim, W.B., Lee, M.G. *Pharmacokinetics of a new carbapenem, DA-1131, after intravenous administration to rabbits with endotoxin-induced pyrexia.* Res Commun Pharmacol Toxicol 1997, 2: 121-8.

15. Kim, S.H., Kim, W.B., Lee, M.G. *Pharmacokinetic changes of a new carbapenem, DA-1131, after intravenous administration to spontaneously hypertensive rats and deoxycorticosterone acetate-salt-induced hypertensive rats.* Drug Metab Dispos 1999, 27: 710-6.

16. Kim, S.H., Kwon, J.W., Kim, W.B., Lee, M.G. *Effects of cilastatin on the pharmacokinetics of a new carbapenem, DA-1131, in rats, rabbits, and dogs.* Antimicrob Agents Chemother 1999, 43: 2524-7.

17. Kim, S.H., Kim, W.B., Lee, M.G. *Effect of probenecid on the renal excretion mechanism of a new carbapenem, DA-1131, in rats and rabbits.* Antimicrob Agents Chemother 1999, 43: 96-9.

18. Kim, S.H., Kim, W.B., Lee, M.G. *No effect of probenecid on the renal excretion mechanism of a new carbapenem, DA-1131, in dogs.* Res Commun Mol Pathol Pharmacol 1998, 101: 85-92.

19. Kim, S.H., Kim, W.B., Kwon, J.W., Lee, M.G. *Nephroprotective effect of betamipron on a new carbapenem, DA-1131, in rabbits.* Biopharm Drug Dispos 1999, 20: 125-9.

20. Kim, S.H., Kwon, J.W., Kim, W.B., Lee, M.G. *Effects of water deprivation for 72 hours on the pharmacokinetics of a new carbapenem, DA-1131, in rats.* Life Sci, submitted.