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In Vitro and In Vivo Antibacterial Activities of S-1090, a New Oral Cephalosporin

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S-1090, a new oral cephalosporin, was active against selected gram-negative bacteria and methicillin-susceptible clinical isolates of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Staphylococcus warneri*, against which it had excellent activity. S-1090 was the most active compound against *Streptococcus pyogenes* and *Streptococcus agalactiae* among the agents compared. The in vivo efficacy of S-1090 against systemic and urinary and respiratory tract infections caused by gram-positive and -negative bacteria was superior to that expected from the in vitro and in vivo activities of the agents against which it was compared.

Recently, new oral cephalosporins, which are esterified with the pivaloyloxymethyl group to improve intestinal absorption, have been developed in Japan. It has been reported that several pivaloyloxymethyl ester derivatives, such as cefteram pivoxil, reduce the amount of carnitine in the body (6, 15). Therefore, it is necessary to administer these drugs with caution to patients with carnitine deficiency (14). A better approach is the development of new oral cephalosporins that are well absorbed without esterification of the pivaloyloxymethyl group, in addition to having broad and potent antibacterial activities. S-1090, (−)-(6*R*,7*R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-8-oxo-3-(1*H*-1,2,3-triazol-4-yl) thiomethylthio-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrochloride monohydrate, is a new synthetic, nonesterified, oral cephalosporin that has been developed to overcome this problem (Fig. 1). In the present study, we compared the in vitro and in vivo potencies of S-1090 with those of cefdinir (11), cefpodoxime (16), cefaclor, cefditoren (8), saropenem (12), amoxicillin, and ofloxacin.

The following antimicrobial agents were obtained from the indicated sources: S-1090 and cefaclor, Shionogi & Co. (Osaka, Japan); cefdinir and amoxicillin, Fujisawa Pharmaceutical Co. (Osaka, Japan); cefpodoxime and cefpodoxime proxetil, Sankyo Co. (Tokyo, Japan); cefditoren and cefditoren pivoxil, Meiji Seika Kaisha (Tokyo, Japan); saropenem, Suntory Co. (Osaka, Japan); and ofloxacin, Daiichi Pharmaceutical Co., (Tokyo, Japan). Since S-1090 is adsorbed by glass or plastic, the antibiotic solution was prepared in a silicone-coated tube (Becton Dickinson & Co., Rutherford, N.J.).

Most bacterial strains used in the present study were clinical isolates collected at Toho University Hospital and were stored at −80°C.

The MICs were determined by the broth microdilution method as described in the guidelines of the Japanese Society for Chemotherapy (1, 2). We used cation-adjusted Mueller-Hinton broth (Difco, Detroit, Mich.) with appropriate concentrations of the divalent cations Ca^{2+} and Mg^{2+} for nonfastidious aerobic bacteria. The broth was supplemented with 5% lysed horse blood for *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Enterococcus faecalis*, *Enterococcus faecium*, and *Moraxella catarrhalis*. We also used cation-adjusted Mueller-Hinton broth supplemented with 5% lysed horse blood, 5 mg of yeast extract (Oxoid, Basingstoke, England) per ml, and 15 μg of NAD (Sigma Chemical Co., St. Louis, Mo.) per ml for *Haemophilus influenzae*. The bactericidal activities of S-1090 and the other agents at four times the MIC for *Escherichia coli* ATCC 25922 were determined. An overnight culture in Mueller-Hinton broth was inoculated into fresh broth, and the mixture was incubated, with constant shaking, until the viability reached 2×10^6 to 3×10^6 CFU/ml. After the addition of antibiotics, the cultures were incubated at 35°C and the number of viable cells was determined.

The potency of S-1090 was determined in a mouse model of bacteremia. Male SLC/ICR mice weighing 18 to 22 g (Sankyo Labo Service Co., Tokyo, Japan) were injected intraperitoneally with a portion of a 0.5-ml dose of a bacterial suspension (approximately 100 times the 50% lethal dose) in either saline or 5% mucin (Difco). S-1090 and the other antibiotics were formulated with 0.5% methylcellulose (Wako Pure Chemical Industries, Osaka, Japan) and were administered orally 1 h after the induction of infection. Mortality was recorded over 7 days to estimate the 50% effective dose (ED_{50}), which was determined by probit analysis (7).

The efficacy of S-1090 against respiratory infection was determined by using a mouse model of intranasal infection with *S. pneumoniae* TUH 39. Under pentobarbital anesthesia (50 mg/kg of body weight), 4-week-old female SLC/ICR mice (body weight, 18 to 22 g; $n = 10$) were infected by instillation of a bacterial suspension. Drugs were administered orally at 12 h after infection twice daily every 12 h for a period of 3 days.

The therapeutic effects of S-1090 and the other agents were tested in a mouse model of ascending urinary tract infection induced by *E. coli* TMS 3 by the method described by Oomori et al. (13). Four-week-old female SLC/ICR mice (weight, 16 to 20 g) were used. Dietary intake was restricted to water for 20 h prior to infection. Under ether anesthesia, a polyethylene catheter (Marukyu, Tokyo, Japan) was introduced transurethrally to inject 0.05 ml of bacterial suspension into the bladder. The urethral catheter was removed immediately after inoculation, and the external urethral meatus was clamped for 1 h. Drugs were administered orally 24 h after infection at dosages ranging from 0.2 to 20 mg/kg twice daily every 12 h for a period of 3 days. Mice were sacrificed 2 days after administra-

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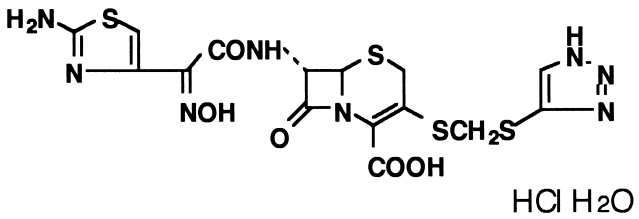

FIG. 1. Chemical structure of S-1090.

tion of the last dose of the test drug, and the number of viable cells in the kidneys was determined.

We examined the in vitro antibacterial activity of S-1090 against 938 recent clinical isolates of gram-positive and gram-negative aerobic bacteria. The MICs at which 50 and 90% of isolates are inhibited (MIC_{50}s and MIC_{90}s, respectively) as well as the MIC range of each drug for the bacteria tested are listed in Table 1. S-1090 was potent against methicillin-susceptible *Staphylococcus aureus* isolates. However, it was less active than saropenem, had activity similar to that of cefdinir, but was more active than the other agents against which it was compared. S-1090 was also active against methicillin-susceptible *Staphylococcus epidermidis* (MIC_{90}, 0.25 μg/ml). S-1090 (MIC_{90}, 0.125 μg/ml) had the same potent activity as cefdinir and saropenem against *Staphylococcus warneri*, but it was more active than the other agents tested. S-1090 was the most active compound among the compounds tested against *S. pyogenes* and *S. agalactiae*. The activity of S-1090 against *S. pneumoniae* was similar to that of cefdinir, but it was twofold more active than cefpodoxime and ofloxacin and was less active than cefditoren, saropenem, and amoxicillin. The potency of S-1090 against gram-negative bacteria was comparable to that of cefdinir but was higher than that of cefdinir against *Morganella morganii*, *Citrobacter freundii*, *Bordetella pertussis*, *Helicobacter pylori*, and *H. influenzae*. S-1090 was the most active compound against *Neisseria gonorrhoeae.*

S-1090 showed bactericidal activity against *E. coli* ATCC 25922 at four times the MIC (Fig. 2). Its bactericidal activity exceeded those of cefdinir, cefpodoxime, and cefaclor.

The in vivo efficacy of S-1090 was compared with those of cefdinir, cefpodoxime proxetil, cefditoren pivoxil, cefaclor, and ofloxacin against experimentally induced acute bacteremia in mice (Table 2). S-1090 against *S. aureus* Smith (ED_{50}, 2.13 mg/kg) was less efficacious than cefaclor, but S-1090 was more effective than cefdinir and ofloxacin. The ED_{50}s of cefpodoxime proxetil and cefditoren pivoxil were both greater than 15 mg/kg against *S. aureus* Smith. S-1090 was the most effective compound against *S. pneumoniae* TUH 39. Against gram-negative pathogens of *E. coli* C-11 and *Klebsiella pneumoniae* 3K-25, the ED_{50}s of S-1090 were less than 5 mg/kg.

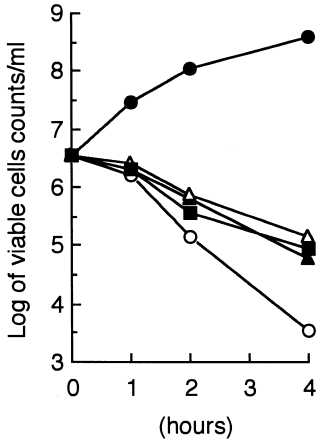

FIG. 2. In vitro killing activity against *E. coli* ATCC 25922. ●, control; ○, S-1090 at four times the MIC (1 μg/ml); ▲, cefdinir at four times the MIC (1 μg/ml); △, cefpodoxime at four times the MIC (2 μg/ml); ■, cefaclor at four times the MIC (8 μg/ml).

Against respiratory tract infections induced by inoculation of *S. pneumoniae* TUH 39, S-1090 was less effective than amoxicillin but was as effective as cefpodoxime proxetil and was more effective than cefdinir (Table 2). Against ascending urinary tract infections induced by inoculation of *E. coli* TMS 3 in mice, the antibacterial activity of S-1090 in mice treated with the drug at 2 or 20 mg/kg per dose was significantly different from that in the control group of mice ($P < 0.05$) but not that in mice treated with the other agents tested (Table 3). Treatment with S-1090 resulted in a greater reduction in the number of organisms compared with that after treatment with cefdinir, cefpodoxime proxetil, and cefaclor.

Oral cephalosporins have been used to treat mild forms of infection, such as dermal and soft tissue infections, urinary tract infections, bronchitis, and otitis media. The main causative organisms in these infections are *S. aureus*, *Staphylococcus epidermidis*, *S. pneumoniae*, *E. coli*, *H. influenzae*, and *K. pneumoniae*. In addition, the clinical significance of other coagulase-negative staphylococci had steadily increased (5). Until recently, these organisms were regarded by clinicians and microbiologists as contaminants present in clinical specimens. Therefore, it is important that orally administered drugs have antibacterial activity against these gram-positive pathogens. In the present study, S-1090 was the most active compound against *S. pyogenes* and *S. agalactiae* and was as active as cefdinir against staphylococci. It was more active than cefdinir against *E. faecalis*. Cefixime, which contains the carboxymethoxyimino aminothiazole side chain at the 7 position, has been demonstrated to be potent against gram-negative pathogens but less active against gram-positive pathogens (3). By introducing the hydroxyimino group instead of the carboxymethoxyimino group in the side chain at position 7, cefdinir became more active than cefixime against gram-positive pathogens (11). While S-1090 has the same side chain as cefdinir at the 7 position, it contains a new triazolthiomethylthio group in the side chain at the 3 position. This side chain has a chemical structure different from that of cefdinir. The chemical structure suggests that new side chain at position 3 enhances the activity of S-1090 against gram-positive organisms. Thus, S-1090 represents an advance in the activities of oral expanded-spectrum cephalosporins against gram-positive and -negative pathogens. This new drug also showed strong bactericidal activity against *E. coli* ATCC 25922; against this strain, the activity of S-1090 was greater than those of cefdinir, cefpodoxime, and cefaclor.

Our results demonstrated that S-1090 is more effective than cefdinir against *S. aureus* Smith and *S. pneumoniae* TUH 39 in systemic infections. Furthermore, S-1090 showed a therapeutic effect against localized infections such as those in the ascending urinary and respiratory tracts. Overall, the in vivo efficacy of S-1090 was better than expected from its in vitro activities and was better than the in vitro and in vivo activities of the other agents tested. One speculation for the reasons for these results is that S-1090 produced higher levels in plasma and a longer half-life in plasma compared with those of the nonester oral cephalosporins in various experimental animals (4) and humans (9). The results of the present study in mice, together with those of pharmacokinetic studies in humans, suggest that

TABLE 1. Antibacterial activities of S-1090, cefdinir, cefpodoxime, cefditoren, saropenem, cefaclor, amoxicillin, and ofloxacin against clinical isolates

Organism (no. of strains)	Drug	MIC (μg/ml)		
		Range	50%	90%
Methicillin susceptible *Staphylococcus aureus* (45)	S-1090	0.125–0.5	0.25	0.25
	Cefdinir	0.125–0.5	0.25	0.25
	Cefpodoxime	1–4	2	4
	Cefditoren	0.25–1	0.5	0.5
	Saropenem	0.063–0.125	0.125	0.125
	Cefaclor	0.5–16	2	8
	Amoxicillin	0.5–128	4	32
	Ofloxacin	0.063–0.5	0.5	0.5
Methicillin-resistant *Staphylococcus aureus* (44)	S-1090	16–64	32	32
	Cefdinir	64–>128	>128	>128
	Cefpodoxime	>128	>128	>128
	Cefditoren	32–128	64	64
	Saropenem	64–>128	>128	>128
	Cefaclor	64–>128	>128	>128
	Amoxicillin	16–>128	64	128
	Ofloxacin	0.25–>128	16	128
Methicillin-susceptible *Staphylococcus epidermidis* (44)	S-1090	0.032–1	0.063	0.25
	Cefdinir	0.032–2	0.063	0.25
	Cefpodoxime	0.125–4	0.5	2
	Cefditoren	0.063–2	0.125	0.5
	Saropenem	0.032–0.5	0.063	0.125
	Cefaclor	0.25–8	0.5	2
	Amoxicillin	0.032–16	0.125	2
	Ofloxacin	0.125–128	0.5	1
Methicillin-resistant *Staphylococcus epidermidis* (36)	S-1090	0.5–64	8	64
	Cefdinir	1–>128	64	>128
	Cefpodoxime	8–>128	32	>128
	Cefditoren	1–128	16	128
	Saropenem	0.125–>128	4	>128
	Cefaclor	4–>128	32	64
	Amoxicillin	2–>128	16	64
	Ofloxacin	0.25–>128	8	>128
Staphylococcus haemolyticus (12)	S-1090	0.25–128	2	128
	Cefdinir	0.25–>128	4	>128
	Cefpodoxime	2–>128	8	>128
	Cefditoren	0.5–>128	4	>128
	Saropenem	0.125–>128	0.25	>128
	Cefaclor	0.5–128	4	128
	Amoxicillin	0.125–>128	8	>128
	Ofloxacin	0.125–64	0.25	32
Staphylococcus warneri (19)	S-1090	0.032–0.125	0.125	0.125
	Cefdinir	0.032–0.125	0.125	0.125
	Cefpodoxime	0.125–2	1	2
	Cefditoren	0.063–0.5	0.25	0.5
	Saropenem	0.032–0.125	0.125	0.125
	Cefaclor	0.25–2	1	2
	Amoxicillin	0.125–1	0.25	1
	Ofloxacin	0.25–8	0.5	1
Other CNS[a] (17)	S-1090	0.032–64	0.125	32
	Cefdinir	0.063–>128	0.25	>128
	Cefpodoxime	0.5–>128	2	>128
	Cefditoren	0.25–128	1	128
	Saropenem	0.063–8	0.125	4
	Cefaclor	0.125–64	2	64
	Amoxicillin	0.063–128	0.5	64
	Ofloxacin	0.25–2	0.5	1
Streptococcus pyogenes (42)	S-1090	0.004–0.016	0.008	0.008
	Cefdinir	0.008–0.032	0.016	0.016
	Cefpodoxime	0.016–0.063	0.032	0.032

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TABLE 1—*Continued*

Organism (no. of strains)	Drug	MIC (μg/ml)		
		Range	50%	90%
	Cefditoren	0.008–0.032	0.016	0.016
	Saropenem	0.016–0.063	0.016	0.032
	Cefaclor	0.125–0.5	0.25	0.25
	Amoxicillin	0.008–0.063	0.016	0.016
	Ofloxacin	0.5–4	2	4
Streptococcus pneumoniae (31)	S-1090	0.004–1	0.063	1
	Cefdinir	0.016–4	0.25	1
	Cefpodoxime	0.016–4	0.25	2
	Cefditoren	0.008–1	0.063	0.5
	Saropenem	0.008–0.5	0.032	0.125
	Cefaclor	0.125–64	1	16
	Amoxicillin	0.008–2	0.032	0.5
	Ofloxacin	1–4	2	2
Streptococcus agalactiae (30)	S-1090	0.016–0.063	0.016	0.032
	Cefdinir	0.032–0.063	0.063	0.063
	Cefpodoxime	0.063–0.125	0.063	0.125
	Cefditoren	0.032–0.063	0.032	0.063
	Saropenem	0.032–0.063	0.063	0.063
	Cefaclor	1–2	2	2
	Amoxicillin	0.063–0.125	0.063	0.125
	Ofloxacin	1–4	2	2
Enterococcus faecalis (29)	S-1090	1–64	4	8
	Cefdinir	2–128	16	128
	Cefpodoxime	64–>128	>128	>128
	Cefditoren	2–>128	128	128
	Saropenem	1–32	2	4
	Cefaclor	64–>128	128	128
	Amoxicillin	0.5–4	1	1
	Ofloxacin	2–128	4	32
Enterococcus faecium (26)	S-1090	1–>128	>128	>128
	Cefdinir	4–>128	>128	>128
	Cefpodoxime	4–>128	>128	>128
	Cefditoren	2–>128	>128	>128
	Saropenem	4–>128	>128	>128
	Cefaclor	16–>128	>128	>128
	Amoxicillin	0.25–>128	32	128
	Ofloxacin	2–>128	8	64
Escherichia coli (30)	S-1090	0.063–4	0.125	0.5
	Cefdinir	0.032–8	0.25	1
	Cefpodoxime	0.063–16	0.5	1
	Cefditoren	0.063–4	0.25	0.5
	Saropenem	0.25–2	0.5	1
	Cefaclor	0.5–128	2	4
	Amoxicillin	0.063–>128	4	>128
	Ofloxacin	0.063–0.25	0.125	0.125
Klebsiella pneumoniae (30)	S-1090	0.063–64	0.125	0.25
	Cefdinir	0.063–>128	0.125	0.25
	Cefpodoxime	0.063–>128	0.25	0.25
	Cefditoren	0.063–32	0.25	0.5
	Saropenem	0.25–8	0.5	1
	Cefaclor	0.5–>128	1	2
	Amoxicillin	32–>128	128	>128
	Ofloxacin	0.125–4	0.25	0.5
Klebsiella oxytoca (35)	S-1090	0.063–8	0.125	1
	Cefdinir	0.063–4	0.125	0.25
	Cefpodoxime	0.125–16	0.25	0.5
	Cefditoren	0.063–0.5	0.25	0.25
	Saropenem	0.25–2	0.5	1
	Cefaclor	0.5–8	1	2
	Amoxicillin	16–>128	128	>128

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TABLE 1—*Continued*

Organism (no. of strains)	Drug	MIC (μg/ml)		
		Range	50%	90%
	Ofloxacin	0.063–0.25	0.125	0.25
Proteus mirabilis (27)	S-1090	0.032–0.125	0.063	0.125
	Cefdinir	0.032–0.25	0.125	0.125
	Cefpodoxime	0.032–0.25	0.125	0.125
	Cefditoren	0.063–0.5	0.125	0.25
	Saropenem	1–8	2	4
	Cefaclor	0.032–4	2	2
	Amoxicillin	0.128–128	1	2
	Ofloxacin	0.125–0.5	0.125	0.25
Proteus vulgaris (36)	S-1090	0.25–>128	128	>128
	Cefdinir	0.5–>128	64	>128
	Cefpodoxime	1–>128	32	>128
	Cefditoren	0.5–>128	32	>128
	Saropenem	2–>128	8	32
	Cefaclor	8–>128	>128	>128
	Amoxicillin	4–>128	>128	>128
	Ofloxacin	0.125–32	0.5	2
Providencia rettgeri (14)	S-1090	0.008–32	0.5	32
	Cefdinir	0.032–64	0.5	32
	Cefpodoxime	0.008–16	0.25	8
	Cefditoren	0.063–64	0.5	16
	Saropenem	0.5–8	2	4
	Cefaclor	4–>128	>128	>128
	Amoxicillin	0.5–>128	64	>128
	Ofloxacin	0.063–>128	8	>128
Morganella morganii (32)	S-1090	0.125–128	4	16
	Cefdinir	0.5–>128	16	32
	Cefpodoxime	0.5–>128	32	128
	Cefditoren	0.25–128	8	64
	Saropenem	2–8	4	8
	Cefaclor	4–>128	>128	>128
	Amoxicillin	8–>128	>128	>128
	Ofloxacin	0.032–128	0.125	0.5
Citrobacter freundii (22)	S-1090	0.125–>128	0.5	4
	Cefdinir	0.25–>128	4	64
	Cefpodoxime	1–>128	2	8
	Cefditoren	0.5–>128	0.5	4
	Saropenem	0.25–8	0.5	1
	Cefaclor	4–>128	64	128
	Amoxicillin	16–>128	64	128
	Ofloxacin	0.063–128	0.25	2
Enterobacter cloacae (29)	S-1090	0.125–>128	4	>128
	Cefdinir	0.125–>128	8	>128
	Cefpodoxime	0.125–>128	2	>128
	Cefditoren	0.25–>128	1	>128
	Saropenem	0.25–8	2	4
	Cefaclor	1–>128	>128	>128
	Amoxicillin	4–>128	>128	>128
	Ofloxacin	0.063–0.5	0.125	0.25
Serratia marcescens (30)	S-1090	8–>128	32	>128
	Cefdinir	4–>128	32	>128
	Cefpodoxime	1–>128	4	64
	Cefditoren	1–>128	2	16
	Saropenem	4–128	8	32
	Cefaclor	>128	>128	>128
	Amoxicillin	64–>128	128	>128
	Ofloxacin	0.125–128	0.5	32
Acinetobacter spp. (25)	S-1090	2–64	4	32
	Cefdinir	2–	4	32

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TABLE 1—*Continued*

Organism (no. of strains)	Drug	MIC (μg/ml)		
		Range	50%	90%
	Cefpodoxime	8–>128	32	128
	Cefditoren	16–>128	32	64
	Saropenem	4–64	16	32
	Cefaclor	8–>128	128	>128
	Amoxicillin	4–>128	16	>128
	Ofloxacin	0.25–128	0.5	2
Alcaligenes denitrificans subsp. *xylosoxydans* (25)	S-1090	0.5–>128	128	>128
	Cefdinir	4–128	>128	>128
	Cefpodoxime	16–>128	>128	>128
	Cefditoren	8–>128	>128	>128
	Saropenem	0.5–>128	16	>128
	Cefaclor	2–>128	>128	>128
	Amoxicillin	8–>128	128	>128
	Ofloxacin	4–>128	64	>128
Moraxella catarrhalis (46)	S-1090	0.063–8	1	2
	Cefdinir	0.125–1	0.5	0.5
	Cefpodoxime	0.125–4	1	2
	Cefditoren	0.063–2	0.25	1
	Saropenem	0.063–1	0.5	1
	Cefaclor	0.063–32	2	16
	Amoxicillin	0.125–16	4	8
	Ofloxacin	0.063–1	0.125	0.125
Haemophilus influenzae (49)	S-1090	0.008–2	0.063	0.125
	Cefdinir	0.032–2	0.5	1
	Cefpodoxime	0.008–4	0.063	0.125
	Cefditoren	0.008–2	0.016	0.125
	Saropenem	0.125–4	0.5	1
	Cefaclor	0.5–32	4	32
	Amoxicillin	0.25–128	0.5	64
	Ofloxacin	0.016–0.5	0.032	0.125
Neisseria gonorrhoeae (18)[b,c]	S-1090	<0.004–0.016	<0.004	0.008
	Cefdinir	<0.004–0.063	<0.004	0.032
	Cefpodoxime	<0.004–0.063	<0.004	0.063
	Cefditoren	<0.004–0.063	<0.004	0.016
	Saropenem	<0.004–0.125	0.063	0.125
	Cefaclor	0.063–0.5	0.125	0.5
	Amoxicillin	0.063–1	0.25	0.5
	Ofloxacin	0.008–0.063	0.008	0.016
Helicobacter pylori (26)[c,d]	S-1090	0.125–0.25	0.125	0.25
	Cefdinir	0.25–2	0.25	2
	Cefpodoxime	2–64	2	64
	Cefditoren	1–8	1	8
	Saropenem	0.063	0.063	0.063
	Cefaclor	0.125–0.25	0.125	0.25
	Amoxicillin	0.063–0.125	0.063	0.063
	Ofloxacin	0.5	0.5	0.5
Bordetella pertussis (52)[c,e]	S-1090	0.125–8	1	2
	Cefdinir	1–64	32	64
	Cefpodoxime	4–16	8	16
	Cefditoren	0.125–2	0.5	0.5
	Saropenem	0.25–8	1	2
	Cefaclor	8–64	32	64
	Amoxicillin	0.5–1	0.5	0.5
	Ofloxacin	0.063–0.5	0.25	0.25
Pseudomonas aeruginosa (30)	S-1090	>128	>128	>128
	Cefdinir	>128	>128	>128
	Cefpodoxime	>128	>128	>128
	Cefditoren	32–>128	>128	>128
	Saropenem	>128	>128	>128
	Cefaclor	>128	>128	>128

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TABLE 1—*Continued*

Organism (no. of strains)	Drug	MIC (μg/ml)		
		Range	50%	90%
	Amoxicillin	>128	>128	>128
	Ofloxacin	1–>128	2	128
Burkholderia cepacia (11)	S-1090	16–>128	128	>128
	Cefdinir	16–>128	128	>128
	Cefpodoxime	32–>128	128	>128
	Cefditoren	16–>128	64	>128
	Saropenem	32–128	64	64
	Cefaclor	>128	>128	>128
	Amoxicillin	128–>128	>128	>128
	Ofloxacin	4–32	16	32
Stenotrophomonas maltophilia (16)	S-1090	>128	>128	>128
	Cefdinir	>128	>128	>128
	Cefpodoxime	>128	>128	>128
	Cefditoren	>128	>128	>128
	Saropenem	>128	>128	>128
	Cefaclor	>128	>128	>128
	Amoxicillin	>128	>128	>128
	Ofloxacin	2–4	4	4

[a] CNS, coagulase-negative staphylococci, including *Staphylococcus saprophyticus* ($n = 5$), *Staphylococcus lugdunensis* ($n = 3$), *Staphylococcus simulans* ($n = 3$), *Staphylococcus hominis* ($n = 2$), *Staphylococcus schleiferi* ($n = 2$), *Staphylococcus captis* ($n = 1$), and *Staphylococcus felis* ($n = 1$).
[b] GC agar (Difco) supplemented with 2% hemoglobin and 1% defined supplement (10) was used to test *Neisseria gonorrhoeae* isolates, which were incubated in 5% CO_2 at 35°C for 24 h.
[c] The MICs were determined by the agar dilution method with an inoculum of 10^4 CFU per spot (10).
[d] Blood agar base no. 2 (Oxoid) was used; it was supplemented with 7% horse blood, and the mixture was incubated under the CampyPak system (BBL, Cockeysville, Md.) at 35°C for 48 h.
[e] Bordet Gengou agar (Difco) supplemented with 15% horse blood and 1% glycerol was used, and the mixture was incubated at 35°C for 48 h.

TABLE 2. Protective effects of S-1090 and comparison agents against systemic infection and respiratory tract infections

Organism	Challenge dose (CFU/mouse)	Drug	ED_{50} (mg/kg) (95% confidence limit)	MIC (μg/ml)
Staphylococcus aureus Smith[a]	4.8×10^7	S-1090	2.13 (1.13–3.82)	0.25
		Cefdinir	6.79 (4.85–11.3)	0.25
		Cefpodoxime proxetil	17.4 (10.2–33.9)	2
		Cefditoren pivoxil	27.7 (16.1–64.3)	0.5
		Cefaclor	1.57 (1.00–4.35)	1
		Ofloxacin	8.21 (4.95–20.4)	0.5
Streptococcus pneumoniae TUH 39[a]	7.0×10^3	S-1090	1.62 (1.23–2.14)	0.063
		Cefdinir	89.1 (66.1–179)	0.25
		Cefpodoxime proxetil	5.90 (4.27–8.24)	0.063
		Cefditoren pivoxil	5.19 (3.80–7.73)	0.032
		Cefaclor	28.6 (20.6–39.6)	0.5
		Ofloxacin	>100	2
Escherichia coli C-11[a]	1.5×10^5	S-1090	0.85 (0.57–1.23)	0.016
		Cefdinir	2.03 (0.65–3.97)	0.063
		Cefpodoxime proxetil	0.42 (0.14–0.70)	0.032
		Cefditoren pivoxil	1.28 (0.69–2.28)	0.008
		Cefaclor	2.28 (1.40–4.68)	0.5
		Ofloxacin	1.11 (0.75–1.62)	0.016
Klebsiella pneumoniae 3K-25[a]	1.2×10^4	S-1090	4.17 (3.10–5.63)	0.125
		Cefdinir	53.6 (38.3–81.7)	0.125
		Cefpodoxime proxetil	9.67 (5.39–13.9)	0.125
		Cefditoren pivoxil	32.7 (23.0–58.5)	0.25
		Cefaclor	51.9 (33.4–107)	1
		Ofloxacin	10.7 (7.69–17.8)	0.125
Streptococcus pneumoniae TUH 39[b]	1.2×10^6	S-1090	1.24 (0.68–1.92)	0.063
		Cefdinir	11.4 (7.45–17.9)	0.25
		Cefpodoxime proxetil	2.15 (1.43–3.16)	0.063
		Amoxicillin	0.71 (0.42–1.15)	0.008

[a] Systemic infection.
[b] Respiratory tract infection.

TABLE 3. Therapeutic effects of S-1090 and comparison agents against urinary tract infection with *E. coli* TMS3 in mice[a]

Drug	Dose (mg/kg)	MIC (μg/ml)	Log CFU/kidney (mean ± SD)[b]
Control			6.81 ± 0.61
S-1090	0.2	0.25	5.22 ± 1.92
	2		2.48 ± 2.30[c]
	20		2.17 ± 1.43[c]
Cefdinir	0.2	0.25	7.27 ± 0.53
	2		5.67 ± 1.89
	20		4.79 ± 1.43
Cefpodoxime proxetil	0.2	0.5	6.58 ± 1.81
	2		5.16 ± 2.75
	20		4.00 ± 1.86
Cefaclor	0.2	2.0	6.80 ± 0.83
	2		6.38 ± 2.10
	20		5.25 ± 2.26

[a] The inoculum was 1.6×10^7 CFU per mouse.
[b] $n = 10$.
[c] $P < 0.05$ compared with the control group. The statistical difference was analyzed by the Tukey multiple comparison test.

S-1090 is a promising oral cephalosporin for the treatment of infections caused by a variety of gram-positive and gram-negative bacteria.

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