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In Vitro Activity of HSR-903, a New Quinolone

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The in vitro activity of the new fluoroquinolone HSR-903 was compared with those of ciprofloxacin, lomefloxacin, sparfloxacin, and levofloxacin. HSR-903 inhibited 90% of methicillin-susceptible and -resistant *Staphylococcus aureus* (MRSA) clinical isolates at 0.78 and 1.56 μg/ml, respectively, and its activity against MRSA was 16-fold higher than those of sparfloxacin and levofloxacin and 64-fold higher than that of ciprofloxacin. The MICs at which 90% of the isolates are inhibited (MIC_{90}s) of HSR-903 for *Streptococcus pyogenes* and penicillin G-susceptible and -resistant *Streptococcus pneumoniae* (PRSP) were 0.10, 0.05, and 0.05 μg/ml, respectively. Against PRSP, the activity of HSR-903 was 4-fold higher than that of sparfloxacin and 32- to 256-fold higher than those of the other quinolones. The MIC_{90} of HSR-903 for *Enterococcus faecalis* was 0.20 μg/ml, and HSR-903 was more active than the other quinolones against enterococci. The activity of HSR-903 against members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* was roughly similar to that of ciprofloxacin and greater than those of the other quinolones. Against *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Helicobacter pylori*, HSR-903 was the most potent of the quinolones tested. The activity of HSR-903 was not affected by the medium, the inoculum size, or the addition of serum, but decreased under acidic conditions, as did those of the other quinolones tested. HSR-903 exhibited rapid bactericidal action and had a good postantibiotic effect on *S. aureus* and *P. aeruginosa*. HSR-903 inhibited supercoiling by DNA gyrase from *Escherichia coli*, but it was much less active against human topoisomerase II.

The fluoroquinolone antibacterial agents have assumed a major role in the therapy of many infectious diseases in the few years since they became available. However, strains resistant to ciprofloxacin (18) and ofloxacin (14), for example, have appeared among gram-positive bacterial species, especially methicillin-resistant *Staphylococcus aureus* (MRSA) (1, 6, 16). Because MRSA is a major problem in hospitals throughout Japan and other countries, a new quinolone with improved activity against gram-positive bacteria while retaining the broad spectrum of activity of ciprofloxacin would be highly desirable. In the present study, we compared the in vitro activity of HSR-903 {(*S*)-(−)-5-amino-7-(7-amino-5-azaspiro[2.4]hept-5-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid methanesulfonate} (Fig. 1), a new fluoroquinolone (12) containing an NH_2 moiety at the C-5 position and a CH_3 moiety at the C-8 position, with those of ciprofloxacin, lomefloxacin (5), sparfloxacin (7), and levofloxacin (15, 17).

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MATERIALS AND METHODS

Bacteria. *S. aureus* Smith, *S. aureus* TA108, *Escherichia coli* KC-14, and *Pseudomonas aeruginosa* E-2 stocked in our laboratory and clinical isolates from several hospitals in Japan were used in this study.

Antimicrobial agents. HSR-903 and lomefloxacin were provided by Hokuriku Seiyaku Co., Ltd. (Fukui, Japan); ciprofloxacin was from Bayer Yakuhin, Ltd. (Osaka, Japan); sparfloxacin was from Dainippon Pharmaceutical Co., Ltd. (Osaka, Japan); and levofloxacin was from Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan).

Susceptibility tests. The MIC was determined by an agar dilution method with sensitivity test agar (STA; Eiken Chemical Co., Ltd., Tokyo, Japan). Streptococci and *Moraxella catarrhalis* were tested in STA supplemented with 10% horse defibrinated blood. *Haemophilus influenzae* was tested in STA supplemented with 5% Bacto Fildes Enrichment (Difco Laboratories, Detroit, Mich.). *Helicobacter pylori* was tested in brain heart infusion agar (Difco) supplemented with 10% horse defibrinated blood. One loopful (5 μl) of an inoculum corresponding to 2×10^6 to 5×10^6 CFU/ml was inoculated on drug-containing agar plates, and the plates were incubated for 18 h at 37°C, except for *H. pylori*, which was incubated under microaerobic conditions with an AnaeroPack Campylo system (Mitsubishi Gas Chemical Company, Inc.) for 42 h at 37°C. The MIC was defined as the lowest drug concentration which prevented visible growth of bacteria. The effects of inoculum size and medium pH, as well as the addition of horse serum, on the activities of quinolones were also determined by the STA dilution method. The effect of the medium was determined by the agar dilution method with nutrient agar (Nissui Seiyaku Co., Ltd., Tokyo, Japan), trypto-soya agar (Nissui), heart infusion agar (Nissui), and STA.

Time-kill study. *S. aureus* Smith, *E. coli* KC-14, and *P. aeruginosa* E-2 were used. An overnight culture of each organism was inoculated in fresh trypto-soya broth (TSB; Nissui), and incubated at 37°C for 2 h. After the 2-h incubation, the strains were exposed to a quinolone concentration of 1/4× to 2× MIC. In parallel, unexposed controls were run. The number of viable bacteria was determined by counting on agar at 0, 1, 2, and 4 h after the start of quinolone exposure.

PAE in vitro. *S. aureus* Smith, *S. aureus* TA108 (MRSA), and *P. aeruginosa* E-2 were used. The test was performed as described previously (2). After an overnight culture of each organism inoculated in fresh TSB (about 10^6 CFU per ml), incubation was carried out at 37°C for 2 h. After the 2-h incubation, the strain was exposed to two drug concentrations (4× and 2× MIC for *S. aureus* or 2× and 1× MIC for *P. aeruginosa*) for 1 h at 37°C. In parallel, unexposed controls were run. After the 1-h incubation, each culture was diluted 1:100. The number of viable bacteria was determined by counting on agar at 0, 1, 2, 3, 4, and 5 h after drug dilution. The postantibiotic effect (PAE) was calculated as the difference in

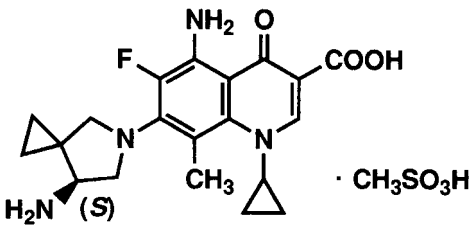

FIG. 1. Chemical structure of HSR-903.

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TABLE 1. Comparative in vitro activities of HSR-903 and other quinolones against clinical isolates

Organism (no. of isolates)	Agent	MIC (μg/ml)[a]		
		Range	50%	90%
MSSA (38)	HSR-903	0.006–6.25	0.025	0.78
	Ciprofloxacin	0.20–100	0.78	6.25
	Lomefloxacin	0.39–>100	0.78	25
	Sparfloxacin	0.025–25	0.10	12.5
	Levofloxacin	0.10–12.5	0.20	12.5
MRSA (33)	HSR-903	0.006–3.13	0.39	1.56
	Ciprofloxacin	0.20–>100	12.5	100
	Lomefloxacin	0.20–>100	25	>100
	Sparfloxacin	0.012–50	3.13	25
	Levofloxacin	0.10–50	6.25	25
Ciprofloxacin-resistant *Staphylococcus aureus* (19)	HSR-903	0.20–3.13	0.78	3.13
	Ciprofloxacin	12.5–>100	100	>100
	Lomefloxacin	25–>100	>100	>100
	Sparfloxacin	1.56–25	3.13	25
	Levofloxacin	3.13–100	12.5	100
Staphylococcus epidermidis (30)	HSR-903	0.006–12.5	0.39	12.5
	Ciprofloxacin	0.20–100	6.25	100
	Lomefloxacin	0.39–>100	50	>100
	Sparfloxacin	0.05–100	3.13	100
	Levofloxacin	0.10–>100	3.13	100
Streptococcus pyogenes (31)	HSR-903	0.025–0.10	0.05	0.10
	Ciprofloxacin	0.39–1.56	0.78	0.78
	Lomefloxacin	3.13–12.5	6.25	6.25
	Sparfloxacin	0.20–0.78	0.39	0.78
	Levofloxacin	0.39–1.56	0.78	1.56
Streptococcus agalactiae (24)	HSR-903	0.05–0.10	0.10	0.10
	Ciprofloxacin	0.78–1.56	0.78	1.56
	Lomefloxacin	6.25–12.5	6.25	12.5
	Sparfloxacin	0.39–0.78	0.39	0.78
	Levofloxacin	0.78–1.56	0.78	1.56
PSSP (28)	HSR-903	0.006–0.20	0.025	0.05
	Ciprofloxacin	0.39–12.5	1.56	3.13
	Lomefloxacin	3.13–25	6.25	12.5
	Sparfloxacin	0.05–0.78	0.20	0.39
	Levofloxacin	0.39–3.13	0.78	1.56
PRSP (21)	HSR-903	0.006–0.10	0.025	0.05
	Ciprofloxacin	0.39–3.13	1.56	3.13
	Lomefloxacin	3.13–12.5	6.25	12.5
	Sparfloxacin	0.05–0.39	0.10	0.20
	Levofloxacin	0.20–1.56	0.78	1.56
Enterococcus faecalis (30)	HSR-903	0.05–0.39	0.10	0.20
	Ciprofloxacin	0.39–3.13	1.56	3.13
	Lomefloxacin	3.13–12.5	6.25	6.25
	Sparfloxacin	0.20–1.56	0.39	0.78
	Levofloxacin	0.39–3.13	0.78	1.56
Enterococcus faecium (19)	HSR-903	0.012–6.25	0.20	1.56
	Ciprofloxacin	0.10–25	1.56	3.13
	Lomefloxacin	1.56–100	6.25	25
	Sparfloxacin	0.10–25	0.78	3.13
	Levofloxacin	0.39–12.5	1.56	3.13
Enterococcus avium (10)	HSR-903	0.012–0.20	0.10	0.10
	Ciprofloxacin	0.20–1.56	0.39	1.56
	Lomefloxacin	1.56–6.25	3.13	6.25
	Sparfloxacin	0.10–0.78	0.39	0.78
	Levofloxacin	0.39–1.56	0.78	1.56

Continued

TABLE 1—*Continued*

Organism (no. of isolates)	Agent	MIC (μg/ml)[a]		
		Range	50%	90%
Escherichia coli (42)	HSR-903	0.006–0.78	0.025	0.05
	Ciprofloxacin	0.012–1.56	0.025	0.05
	Lomefloxacin	0.10–6.25	0.20	0.39
	Sparfloxacin	0.012–1.56	0.05	0.10
	Levofloxacin	0.025–1.56	0.05	0.10
Citrobacter freundii (36)	HSR-903	0.012–50	0.39	1.56
	Ciprofloxacin	0.006–100	0.10	0.78
	Lomefloxacin	0.10–>100	0.78	3.13
	Sparfloxacin	0.05–>100	1.56	6.25
	Levofloxacin	0.05–100	0.39	3.13
Klebsiella pneumoniae (44)	HSR-903	0.012–0.78	0.05	0.10
	Ciprofloxacin	0.012–3.13	0.05	0.10
	Lomefloxacin	0.10–12.5	0.39	0.39
	Sparfloxacin	0.025–3.13	0.10	0.20
	Levofloxacin	0.05–3.13	0.10	0.20
Enterobacter cloacae (39)	HSR-903	≦0.0015–0.78	0.025	0.05
	Ciprofloxacin	0.003–0.78	0.025	0.10
	Lomefloxacin	0.025–3.13	0.20	0.39
	Sparfloxacin	0.003–3.13	0.05	0.20
	Levofloxacin	0.006–0.78	0.10	0.10
Enterobacter aerogenes (39)	HSR-903	0.012–0.10	0.05	0.10
	Ciprofloxacin	0.012–0.05	0.05	0.05
	Lomefloxacin	0.10–0.39	0.20	0.39
	Sparfloxacin	0.025–0.20	0.10	0.20
	Levofloxacin	0.05–0.20	0.10	0.20
Serratia marcescens (44)	HSR-903	0.05–25	0.78	6.25
	Ciprofloxacin	0.05–50	3.13	25
	Lomefloxacin	0.20–>100	6.25	100
	Sparfloxacin	0.10–100	3.13	50
	Levofloxacin	0.10–50	3.13	25
Proteus vulgaris (39)	HSR-903	0.025–0.20	0.10	0.10
	Ciprofloxacin	0.012–0.10	0.025	0.05
	Lomefloxacin	0.10–0.78	0.20	0.39
	Sparfloxacin	0.10–0.78	0.20	0.39
	Levofloxacin	0.025–0.20	0.05	0.20
Proteus mirabilis (40)	HSR-903	0.05–6.25	0.05	0.20
	Ciprofloxacin	0.012–25	0.025	0.20
	Lomefloxacin	0.20–100	0.39	0.78
	Sparfloxacin	0.10–50	0.20	0.39
	Levofloxacin	0.05–25	0.10	0.20
Providencia rettgeri (33)	HSR-903	0.012–12.5	0.20	3.13
	Ciprofloxacin	0.025–>100	0.20	12.5
	Lomefloxacin	0.20–>100	1.56	25
	Sparfloxacin	0.05–50	1.56	12.5
	Levofloxacin	0.05–100	1.56	12.5
Morganella morganii (37)	HSR-903	≦0.0015–0.39	0.05	0.10
	Ciprofloxacin	0.006–3.13	0.025	0.025
	Lomefloxacin	0.025–6.25	0.20	0.20
	Sparfloxacin	0.006–1.56	0.20	0.39
	Levofloxacin	0.006–1.56	0.05	0.20
Pseudomonas aeruginosa (93)	HSR-903	0.10–>100	0.39	6.25
	Ciprofloxacin	0.10–>100	0.39	6.25
	Lomefloxacin	0.39–>100	3.13	100
	Sparfloxacin	0.39–>100	1.56	50
	Levofloxacin	0.20–>100	1.56	25

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TABLE 1—*Continued*

Organism (no. of isolates)	Agent	MIC (μg/ml)[a]		
		Range	50%	90%
Acinetobacter calcoaceticus (28)	HSR-903	≦0.0015–0.10	0.012	0.05
	Ciprofloxacin	0.025–1.56	0.20	0.39
	Lomefloxacin	0.10–3.13	0.39	0.78
	Sparfloxacin	0.006–0.20	0.012	0.05
	Levofloxacin	0.025–0.78	0.10	0.20
Haemophilus influenzae (25)	HSR-903	≦0.0015–0.012	0.003	0.006
	Ciprofloxacin	0.006–0.012	0.012	0.012
	Lomefloxacin	0.025–0.10	0.05	0.05
	Sparfloxacin	≦0.0015–0.012	0.006	0.012
	Levofloxacin	0.012–0.025	0.012	0.025
Moraxella catarrhalis (23)	HSR-903	0.006–0.012	0.012	0.012
	Ciprofloxacin	0.025–0.05	0.05	0.05
	Lomefloxacin	0.10–0.20	0.20	0.20
	Sparfloxacin	0.012–0.025	0.012	0.025
	Levofloxacin	0.05	0.05	0.05
Helicobacter pylori (19)	HSR-903	0.05–3.13	0.20	3.13
	Ciprofloxacin	0.39–50	0.78	25
	Sparfloxacin	0.25–25	0.78	12.5
	Levofloxacin	0.39–12.5	0.78	12.5

[a] 50% and 90%, MIC_{50} and MIC_{90}, respectively.

time between test and control cultures for the organisms to increase in number by a factor of 10, and equation 1 was applied: $PAE = T - C$. T is the time required for the number of organisms in the antibiotic-exposed test culture to increase 10-fold after drug dilution, and C is the time required for the number of organisms in the control culture to increase 10-fold. Each experiment was repeated three times for each quinolone-bacterial strain combination. The data are expressed as means ± standard errors of the means.

Inhibition of DNA gyrase and human topoisomerase II. DNA gyrase was purified from *E. coli* KL-16 as described previously (13), and topoisomerase II from human placenta was purchased from TopoGEN, Inc. The assay for the inhibition of DNA supercoiling activity of DNA gyrase was performed as described previously (13), and the assay for the inhibition of DNA-relaxing activity of topoisomerase II was performed as described in TopoGEN's manual. Assays were run in duplicate, and the mean values are given in Table 3.

RESULTS

Antibacterial activity. The activity of HSR-903 against clinical isolates is shown in Table 1. The MICs at which 90% of the isolates are inhibited (MIC_{90}s) of HSR-903 for methicillin-susceptible *S. aureus* (MSSA; MIC of methicillin, ≤6.25 μg/ml), MRSA (MIC of methicillin, >6.25 μg/ml), ciprofloxacin-resistant *S. aureus* (MIC of ciprofloxacin, >6.25 μg/ml), and *Staphylococcus epidermidis* were 0.78, 1.56, 3.13, and 12.5 μg/ml, respectively. The activity of HSR-903 against MSSA was 16-fold higher than that of sparfloxacin, 8-fold higher than that of ciprofloxacin, and 16- to 32-fold higher than those of the other quinolones at the MIC_{90}s. The activity of HSR-903 against MRSA was 16-fold higher than those of sparfloxacin and levofloxacin and 64-fold higher than that of ciprofloxacin. Against ciprofloxacin-resistant *S. aureus*, the activity of HSR-903 was 8-fold higher than that of sparfloxacin and 32-fold higher than that of levofloxacin. Against *S. epidermidis*, HSR-903 was more active than the other quinolones.

The MIC_{90}s of HSR-903 for *Streptococcus pyogenes*, *Streptococcus agalactiae*, penicillin G-susceptible *Streptococcus pneumoniae* (PSSP; MIC of penicillin G, ≤0.05 μg/ml), and penicillin G-resistant *S. pneumoniae* (PRSP; MIC of penicillin G, >0.05 μg/ml) were 0.10, 0.10, 0.05, and 0.05 μg/ml, respectively. Against *S. pyogenes* and *S. agalactiae*, the activity of HSR-903 was 8-fold higher than that of sparfloxacin and 8- to 128-fold higher than those of the other quinolones. Against PSSP, the activity of HSR-903 was 8-fold higher than that of sparfloxacin and 32- to 256-fold higher than those of the other quinolones. Against PRSP, the activity of HSR-903 was 4-fold higher than that of sparfloxacin and 32- to 256-fold higher than those of the other quinolones.

The MIC_{90}s of HSR-903 for *Enterococcus faecalis*, *Enterococcus faecium*, and *Enterococcus avium* were 0.20, 1.56, and 0.10 μg/ml, respectively. Against enterococci, HSR-903 was more active than the other quinolones.

Among members of the family *Enterobacteriaceae*, HSR-903 inhibited *E. coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Proteus vulgaris*, *Proteus mirabilis*, and *Morganella morganii*, for which the MIC_{90}s were 0.20 μg/ml or less. HSR-903 inhibited *Citrobacter freundii*, *Serratia marcescens*, and *Providencia rettgeri*, for which the MIC_{90}s were 1.56, 6.25, and 3.13 μg/ml, respectively. The activity of HSR-903 was similar to that of ciprofloxacin and greater than those of the other quinolones, but against *Serratia marcescens* and *P. rettgeri*, HSR-903 was superior to ciprofloxacin and the other quinolones.

The MIC_{90} of HSR-903 for *P. aeruginosa* was 6.25 μg/ml. The activity of HSR-903 was similar to that of ciprofloxacin and greater than those of the other quinolones. *Acinetobacter calcoaceticus* was inhibited by HSR-903 at a MIC_{90} of 0.05 μg/ml. *Haemophilus influenzae* and *Moraxella catarrhalis* were inhibited by HSR-903 at MIC_{90}s of 0.006 and 0.012 μg/ml, respectively. HSR-903 was superior to the other quinolones. *H. pylori* was inhibited by HSR-903 at a MIC_{90} of 3.13 μg/ml, and the activity of HSR-903 was stronger than those of the other quinolones.

Factors affecting activity. The activities of HSR-903 against *S. aureus* Smith, *E. coli* KC-14, and *P. aeruginosa* E-2 were similar in all four different media examined (STA, trypto-soya agar, heart infusion agar, and nutrient agar [data not shown]). Changing the pH of STA to 7 and 8, adding horse serum to concentrations of 10, 25, and 50% to the medium, or increasing the inoculum size from 10^3 to 10^6 CFU/spot had no remarkable effect on the activity of HSR-903 against each strain (data not shown). However, the activities in pH 6 STA against *S. aureus* Smith, *E. coli* KC-14, and *P. aeruginosa* E-2 were 4-, 64-, and 8-fold lower, respectively, than those in the pH 7 STA, as were the activities of the other quinolones tested.

Time-kill study. The time-kill curves of HSR-903 were compared with those of ciprofloxacin and levofloxacin against *S. aureus* Smith, *E. coli* KC-14, and *P. aeruginosa* E-2. HSR-903, like the other quinolones, was highly bactericidal at the MIC or higher concentrations for all of the strains tested (Fig. 2).

PAE in vitro. In vitro PAEs of HSR-903 were compared with those of ciprofloxacin and levofloxacin for *S. aureus* Smith and *S. aureus* TA108 (MRSA) at 2× and 4× MIC for 1 h and for *P. aeruginosa* E-2 at 1× and 2× MIC for 1 h. HSR-903 had a PAE of about 1.4 h for *S. aureus* Smith. For *S. aureus* TA108 (MRSA), the PAEs of HSR-903 were 1.9 h (2× MIC) and 1.7 h (4× MIC). For *P. aeruginosa* E-2, the PAEs of HSR-903 were 1.6 h (1× MIC) and 2.0 h (2× MIC). HSR-903 showed the best PAEs among the quinolones tested (Table 2).

Inhibition of DNA gyrase and human topoisomerase II. The inhibitory effects of quinolones on the supercoiling activity of DNA gyrase from *E. coli* KL-16 and the relaxing activity of topoisomerase II from human placenta are shown in Table 3. The assays were run in duplicate. The 50% inhibitory concentrations of HSR-903 for DNA gyrase and human topoisomerase II were 0.74 and 786 μg/ml, respectively. Thus, HSR-903 efficiently inhibited supercoiling by DNA gyrase but was less active against human topoisomerase II. The DNA gyrase-in-

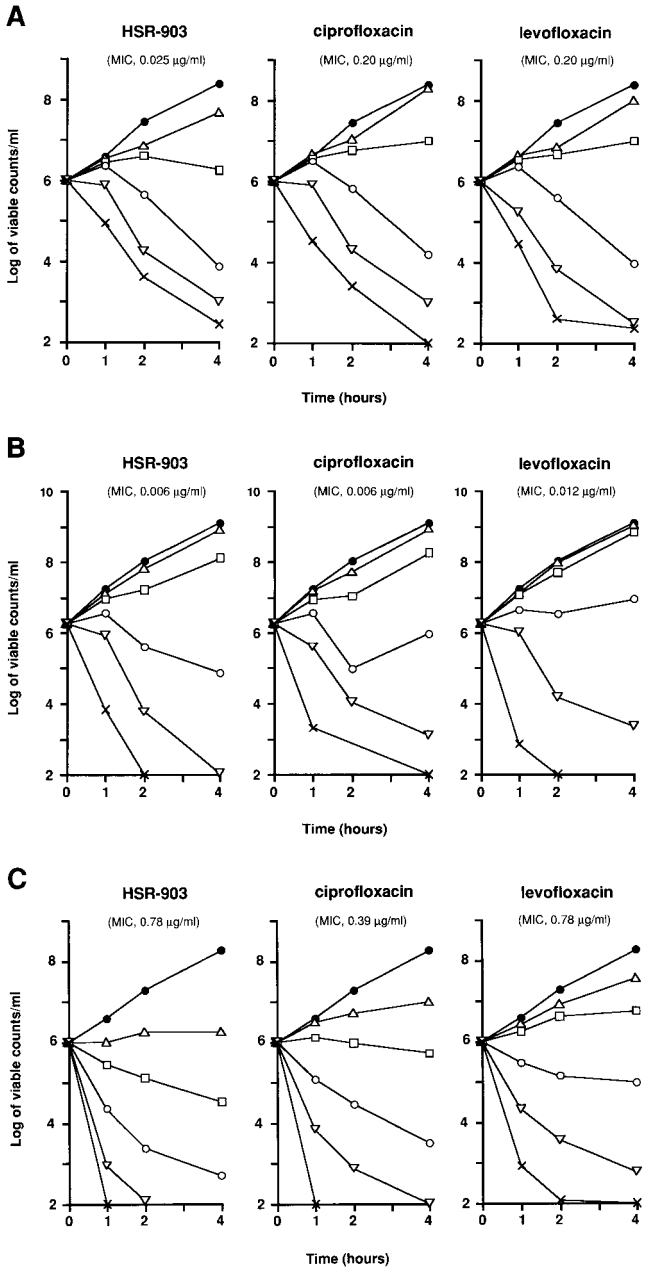

FIG. 2. Bactericidal kinetics of HSR-903, ciprofloxacin, and levofloxacin against *S. aureus* Smith (A), *E. coli* KC-14 (B), and *P. aeruginosa* E-2 (C). Symbols indicate inhibitory concentrations as follows: ●, control; △, 1/4× MIC; □, 1/2× MIC; ○, MIC; ▽, 2× MIC; X, 4× MIC.

hibitory activity of HSR-903 was similar to those of ciprofloxacin, sparfloxacin, and levofloxacin, but the topoisomerase II-inhibitory activity of HSR-903 was weaker than those of ciprofloxacin and sparfloxacin.

DISCUSSION

Our results showed that HSR-903 was more active against staphylococci, streptococci, and enterococci than ciprofloxacin, lomefloxacin, sparfloxacin, and levofloxacin. In particular, HSR-903 exhibited potent activity against MSSA, MRSA, PSSP, PRSP, and *E. faecalis*. Moreover, it was effective against clinical pathogens of the family *Enterobacteriaceae*, *P. aeruginosa*, *H. influenzae*, and *M. catarrhalis*. Against *H. pylori*, one of the etiologic agents of peptic ulcer, the activity of HSR-903 was greater than those of the other quinolones. HSR-903 showed rapid bactericidal action and had good PAEs for *S. aureus* and *P. aeruginosa*. HSR-903 inhibited supercoiling by DNA gyrase from *E. coli* KL-16 but was less active against the human topoisomerase II.

The distinctive structural features of HSR-903 are an NH_2 moiety at the C-5 position, an aminopyrrolidinyl ring at the C-7 position, and a CH_3 moiety at the C-8 position. In general, a 5-NH_2 moiety, as found in sparfloxacin, enhances potency against gram-positive bacteria (3, 8). The 7-aminopyrrolidinyl ring, as found in tosufloxacin (4) and clinafloxacin (11), also enhances potency against gram-positive bacteria (3, 8). In HSR-903, these substituents presumably contribute to the strong activity against gram-positive bacteria. Few quinolones have a CH_3 moiety at the C-8 position, and its effect is not clear. In HSR-903, the 8-CH_3 moiety would contribute to the high hydrophobicity (partition coefficients, measured under the same conditions, were as follows: HSR-903, 2.58; ciprofloxacin, 0.09; levofloxacin, 0.48; and sparfloxacin, 1.14 [*n*-octanol–pH 7.4 Sörensen buffer]). Quinolones with high hydrophobicity, such as sparfloxacin, are reported to be active against a *norA*-me-

TABLE 2. PAEs of quinolones in vitro[a]

Organism	Agent	Concn (μg/ml)	PAE (h)
S. aureus Smith	HSR-903	0.05	1.4 ± 0.1
		0.10	1.4 ± 0.1
	Ciprofloxacin	0.39	1.0 ± 0.1
		0.78	1.1 ± 0.1
	Levofloxacin	0.39	0.9 ± 0.3
		0.78	0.5 ± 0.1
S. aureus TA108 (MRSA)	HSR-903	0.78	1.9 ± 0.2
		1.56	1.7 ± 0.1
	Ciprofloxacin	25	0.7 ± 0.4
		50	0.7 ± 0.3
	Levofloxacin	12.5	1.4 ± 0.2
		25	1.3 ± 0.2
P. aeruginosa E-2	HSR-903	0.78	1.6 ± 0.2
		1.56	2.0 ± 0.2
	Ciprofloxacin	0.39	0.9 ± 0.2
		0.78	1.5 ± 0.1
	Levofloxacin	0.78	0.7 ± 0.1
		1.56	1.3 ± 0.2

[a] The quinolones were tested against organisms after 1 h of exposure to broth containing quinolones at 2× and 4× MIC for *S. aureus* or 1× and 2× MIC for *P. aeruginosa*. Values are means ± standard errors ($n = 3$).

TABLE 3. Inhibitory effects of quinolones on DNA gyrase and topoisomerase II

Agent	MIC (μg/ml)[a]	IC_{50} (μg/ml)[b]	
		DNA gyrase[c]	Topoisomerase II[d]
HSR-903	0.012	0.74	786
Ciprofloxacin	0.025	0.86	398
Levofloxacin	0.05	0.90	1,559
Sparfloxacin	0.025	0.87	400

[a] MIC for *E. coli* KL-16.
[b] IC_{50}, 50% inhibitory concentration.
[c] From *E. coli* KL-16. Measured by DNA supercoiling assay.
[d] From human placenta. Measured by DNA relaxation assay.

diated resistant strain (10, 19). One of the reasons why the antibacterial activity ratio of HSR-903 to ciprofloxacin is greater for MRSA and ciprofloxacin-resistant *S. aureus* than that for MSSA is considered to be that HSR-903, with its high hydrophobicity, is little influenced by NorA.

After oral administration to animals, HSR-903 is well absorbed and is distributed into various tissues, including lung and kidney, but not the central nervous system (9). HSR-903 did not induce convulsions when administered with 4-biphenylacetic acid in mice (12). Moreover, HSR-903 (30 mg/kg, intravenously) did not cause phototoxicity in guinea pigs (12). If HSR-903 behaves similarly in humans, it could prove to be an effective drug against various infections, especially respiratory tract infections. Clinical studies of HSR-903 are in progress.

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