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A-61827 (A-60969), a New Fluoronaphthyridine with Activity against Both Aerobic and Anaerobic Bacteria

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A-61827 (A-60969 is the hydrochloric salt of A-61827) is a new aryl-fluoronaphthyridine which is active against aerobic and anaerobic bacteria. The MICs of A-61827 for 90% of strains (MIC_{90}) of staphylococci and streptococci were ≤1 μg/ml and were generally 1 to 4 twofold dilutions less than those of ciprofloxacin for these bacteria. The MIC_{90}s of A-61827 for members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* were also ≤1 μg/ml. Ciprofloxacin was 1 to 3 twofold dilutions more active than A-61827 against these gram-negative bacteria. *Neisseria gonorrhoeae*, *Campylobacter jejuni*, and *Haemophilus influenzae* were susceptible to <0.06 μg of A-61827 per ml. The MIC_{90} of A-61827 for *Legionella pneumophila* was 0.25 μg/ml. A-61827 was as potent or 1 to 2 twofold dilutions more potent than ciprofloxacin against these organisms. The MIC_{90} of A-61827 for all anaerobic bacteria was ≤4 μg/ml compared with ≤32 μg/ml for ciprofloxacin. In mouse protection tests, A-61827 was as active as ciprofloxacin against *Escherichia coli*, *P. aeruginosa*, and *Salmonella typhimurium* and 5 to 10 times more active than ciprofloxacin against *Staphylococcus aureus* and *Streptococcus pyogenes*. A-61827 was as active as ciprofloxacin against *P. aeruginosa* in a mouse pyelonephritis model and more active than ciprofloxacin and metronidazole in a mouse *Bacteroides fragilis* abscess model. After oral administration of 100 mg/kg to mice, the peak concentrations of A-61827 and ciprofloxacin in serum were 2.3 and 2.4 μg/ml and the half-lives in serum were 3.9 and 1.2 h, respectively.

Several new fluoroquinolones have been previously described (1; H. C. Neu, Antimicrob. Newsl. **4**:9–14, 1987). The quinolones for which most clinical data are available, such as norfloxacin, ofloxacin, enoxacin, and ciprofloxacin, have less than optimal activity against streptococci (1). In addition, they do not have significant activity against many gram-negative anaerobic bacteria (5). A-61827 (Fig. 1) (A-60969 is the HCl salt of A-61827) is a recently described aryl-fluoronaphthyridine which has potent activity against aerobic and anaerobic bacteria in vitro and in vivo (J. Stamm, C. Vojtko, J. Weisz, C. Hanson, D. T. W. Chu, and P. B. Fernandes, Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 132, 1985; P. B. Fernandes, R. R. Bower, K. Jarvis, R. Swanson, and D. T. W. Chu, 25th ICAAC, abstr. no. 133, 1985). The activity of this compound, relative to ciprofloxacin, is described in greater detail in this paper.

MATERIALS AND METHODS

Bacterial strains. The bacterial strains used in this study were clinical isolates maintained frozen at −60°C.

Antibacterial agents. A-61827 and ciprofloxacin were synthesized at Abbott Laboratories, Abbott Park, Ill. Solutions of ciprofloxacin were prepared in water. Since the free base A-61827 is poorly soluble in water, A-60969, the HCl salt, was used for in vitro tests. Stock solutions at a concentration of 100 μg of base per ml were prepared in water by being heated in a boiling-water bath. For in vivo tests, the sulfate salt of A-61827 was used instead of the HCl salt because of the higher solubility of the former. Stock solutions containing 2 mg of base per ml were prepared for in vivo tests. Metronidazole (G. D. Searle and Co., Skokie, Ill.) was dissolved in sterile water to a concentration of 4 mg/ml and was neutralized with 8.5% sodium bicarbonate.

Susceptibility testing. MICs were determined by the agar dilution method described by the National Committee for Clinical Laboratory Standards, with 10^4 CFU per spot as the inoculum (6). Mueller-Hinton agar (MHA), pH 7.3, was used for nonfastidious organisms such as gram-negative enteric bacteria, staphylococci, and enterococci. MHA supplemented with 5% (vol/vol) sheep blood was used for streptococci and *Branhamella catarrhalis*. MHA supplemented with 3% lysed horse blood and 0.001% NAD was used for *Haemophilus influenzae*. *Neisseria gonorrhoeae* was tested on proteose no. 3 agar supplemented with 1% bovine hemoglobin and 1% (vol/vol) Kellogg supplement. *Legionella pneumophila* was tested on buffered charcoal-yeast extract agar. *N. gonorrhoeae* and *L. pneumophila* were tested in the presence of 5% CO_2; *H. influenzae* was tested in an aerobic atmosphere. *Campylobacter* species were tested on MHA and were incubated in a microaerophilic atmosphere by using the Campy-Pak system (BBL Microbiology Systems, Cockeysville, Md.). Anaerobic bacteria were tested by the agar dilution method in Wilkins-Chalgren agar as described

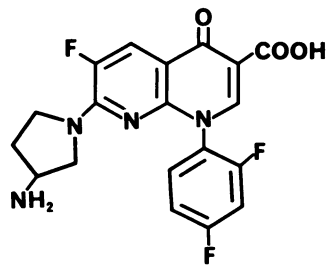

FIG. 1. Chemical structure of A-61827.

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TABLE 1. Comparative in vitro activities of A-61827 and ciprofloxacin

Taxon (no. of strains) and compound	MIC (μg/ml)[a]		
	Range	50%	90%
Escherichia coli (23)			
A-61827	≤0.008–0.25	0.015	0.03
Ciprofloxacin	≤0.008–0.06	0.008	≤0.03
Salmonella-Shigella species (20)			
A-61827	≤0.008–0.03	≤0.008	0.03
Ciprofloxacin	≤0.008–0.015	≤0.008	0.008
Citrobacter species (12)			
A-61827	≤0.008–0.25	0.03	0.06
Ciprofloxacin	≤0.008–0.12	0.008	0.03
Klebsiella species (14)			
A-61827	≤0.008–0.25	0.03	0.06
Ciprofloxacin	≤0.008–0.12	0.015	0.03
Enterobacter species (13)			
A-61827	0.015–0.12	0.03	0.06
Ciprofloxacin	≤0.008–0.03	0.015	0.03
Serratia species (10)			
A-61827	0.03–0.5	0.12	0.25
Ciprofloxacin	≤0.008–0.06	0.03	0.06
Proteus-Morganella species (21)			
A-61827	0.03–0.25	0.12	0.25
Ciprofloxacin	≤0.008–0.03	0.015	0.03
Providencia species (14)			
A-61827	≤0.008–1	0.015	0.12
Ciprofloxacin	≤0.008–0.25	≤0.008	0.12
Pseudomonas aeruginosa (21)			
A-61827	0.03–2	0.25	1
Ciprofloxacin	0.06–0.5	0.12	0.25
Pseudomonas species (13)[b]			
A-61827	0.03–8	0.5	2
Ciprofloxacin	0.06–2	0.25	1
Haemophilus influenzae (12)			
A-61827	0.008–0.015	0.008	0.015
Ciprofloxacin	0.008–0.015	0.008	0.015
Campylobacter species (14)[c]			
A-61827	0.015–0.12	0.03	0.06
Ciprofloxacin	0.06–1	0.12	0.25
Branhamella catarrhalis (16)			
A-61827	0.008–0.015	0.015	0.015
Ciprofloxacin	0.03–0.03	0.03	0.03
Neisseria gonorrhoeae (17)[d]			
A-61827	0.004–0.06	0.008	0.03
Ciprofloxacin	≤0.008–0.12	≤0.008	0.06
Legionella pneumophila (11)			
A-61827	0.25–0.5	0.25	0.25
Ciprofloxacin	0.5–1	0.5	1
Staphylococcus aureus (18)[e]			
A-61827	≤0.008–0.5	0.03	0.03
Ciprofloxacin	0.03–0.5	0.25	0.25
Coagulase-negative staphylococci (13)			
A-61827	≤0.008–0.12	0.06	0.12
Ciprofloxacin	0.03–0.5	0.25	0.5

Continued

TABLE 1—*Continued*

Taxon (no. of strains) and compound	MIC (μg/ml)[a]		
	Range	50%	90%
Streptococcus pyogenes (12)			
A-61827	0.06–0.25	0.12	0.25
Ciprofloxacin	0.12–1	0.5	1
Streptococcus pneumoniae (12)			
A-61827	0.06–1	0.5	0.5
Ciprofloxacin	0.5–2	2	2
Streptococcus agalactiae (14)			
A-61827	0.12–0.5	0.25	0.5
Ciprofloxacin	0.5–2	0.5	1
Streptococcus species (viridans group) (13)			
A-61827	0.06–1	0.25	0.5
Ciprofloxacin	0.5–4	2	4
Enterococcus species (12)			
A-61827	0.25–1	0.5	1
Ciprofloxacin	0.5–2	1	2
Bacteroides fragilis (11)			
A-61827	0.5–2	1	1
Ciprofloxacin	2–8	4	8
Other *Bacteroides* species (10)[f]			
A-61827	0.5–2	0.5	2
Ciprofloxacin	2–32	8	32
Clostridium perfringens (12)			
A-61827	0.12–0.5	0.25	0.25
Ciprofloxacin	0.25–0.5	0.5	0.5
Clostridium difficile (17)			
A-61827	2–4	2	4
Ciprofloxacin	8–16	16	16
Peptococcus-Peptostreptococcus species (14)			
A-61827	0.12–0.25	0.25	0.25
Ciprofloxacin	0.12–2	1	2

[a] 50% and 90%, MIC for 50 and 90% of isolates, respectively.
[b] Includes five strains of *P. pseudoalcaligenes*, four strains of *P. maltophilia*, three strains of *P. fluorescens*, and one strain of *P. cepacia*.
[c] Includes 13 strains of *C. jejuni* and 1 strain of *C. coli*.
[d] Includes 16 β-lactamase-negative strains and 1 β-lactamase-positive strain.
[e] Includes four methicillin-resistant strains.
[f] Includes four strains of *B. thetaiotaomicron*, two strains of *B. vulgatus*, and one strain each of *B. bivius*, *B. disiens*, *B. loescheii*, and *B. melaninogenicus*.

by the National Committee for Clinical Laboratory Standards (7), with 2×10^5 to 6×10^5 CFU per spot as the inoculum. All agar plates were incubated at 35°C.

Effect of serum, urine, pH, and cations on in vitro potency. The effects of human serum, human urine, and pH at 6.5, 7.2, and 8.0 on the in vitro potency of A-61827 and ciprofloxacin were determined as described by Stamm et al. (8). The effects of Ca^{2+} and Mg^{2+} on MICs of compounds for one strain each of *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* were determined by a broth microdilution method. MICs were determined with unsupplemented Mueller-Hinton broth (MHB) and in MHB supplemented with 50, 200, or 400 μg of Ca^{2+} as $CaCl_2$ per ml or 25, 122, or 243 μg of Mg^{2+} as $MgCl_2$ per ml.

Time-kill studies. The bactericidal activity of A-61827 against *E. coli* Juhl (MIC, 0.015 μg/ml) was determined. A total of 1 ml of a logarithmic-phase culture was added to 250-ml flasks containing 19 ml of MHB to yield a final cell density of approximately 5×10^5 CFU/ml. A-61827 was added to separate flasks before inoculation to achieve a final concentration of four or eight times the MIC. At selected time intervals, samples (0.5 ml) were aseptically removed and serially diluted in 10-fold increments in 0.1% Trypticase soy broth (BBL) for viable-cell counting on drug-free agar; to eliminate the effect of drug carry-over, a minimum dilution of 1:200 was used.

Frequency of resistance. The frequency of spontaneous resistance development by three bacterial strains, *E. coli* Juhl, *S. aureus* CMX 730A, and *P. aeruginosa* 5007, to A-61827 was determined as described previously (3). The inoculum (in CFU) was 2.7×10^9 for *E. coli*, 4.1×10^9 for *S. aureus*, and 3.2×10^9 for *P. aeruginosa*.

Mouse protection tests. The in vivo potency of A-61827 was compared with that of ciprofloxacin in mouse protection tests. The test procedures and statistical methods for calculating 50% effective dose and relative potency have been described previously (2).

Experimental pyelonephritis. The kidneys of mice were

TABLE 2. Effect of serum on the in vitro potency of A-61827 and ciprofloxacin

Organism	Compound	MIC (μg/ml)		Twofold difference
		MHB	MHB plus serum	
Staphylococcus aureus 503A	A-61827	0.03	0.12	2
	Ciprofloxacin	0.25	2.0	3
Enterococcus faecalis 579F	A-61827	0.5	0.5	0
	Ciprofloxacin	1.0	2.0	1
Escherichia coli Juhl	A-61827	0.015	0.06	2
	Ciprofloxacin	0.008	0.03	2
Serratia marcescens 541	A-61827	0.12	0.25	1
	Ciprofloxacin	0.03	0.06	1
Proteus mirabilis 502A	A-61827	0.12	0.25	1
	Ciprofloxacin	0.015	0.03	1
Pseudomonas aeruginosa 548	A-61827	0.12	0.12	0
	Ciprofloxacin	0.06	0.5	3
Acinetobacter species 675B	A-61827	0.015	0.25	4
	Ciprofloxacin	0.06	0.25	2

infected with *P. aeruginosa* 5007 as described previously (2). Twenty-four hours after infections, groups of 10 mice were treated orally by gavage with a single dose of 6.3, 25, or 100 mg of A-61827 or ciprofloxacin per kg. One group of mice was left untreated as infection controls. The kidneys were homogenized and cultured quantitatively 24 h after treatment. The total number of viable bacteria in the two kidneys of each animal was determined, and the geometric mean ± standard error of the mean of the viable-bacterium counts for two kidneys was calculated for each group of mice.

Experimental anaerobic abscess model. A subcutaneous anaerobic abscess model for mice was used to test the efficacy of A-61827 against *Bacteroides fragilis* in vivo. The method has been described previously (4) except that C3H mice (Charles River Breeding Laboratories, Inc., Wilmington, Mass.) were used. The mice were treated with A-61827, ciprofloxacin, or metronidazole subcutaneously at 1 h after infection, followed by treatment twice a day for 4 days. The daily doses were administered 8 h apart. The doses were 3.1, 12.5, and 50 mg/kg. Each dose was tested in groups of five mice. The abscesses were excised and cultured quantitatively at 18 h after the last injection. The geometric means of viable-bacterium counts in the abscesses were calculated and compared with those of untreated mice.

Pharmacokinetic studies. A-61827 and ciprofloxacin were each administered to mice as single doses of 100 mg/kg orally by gavage or 10 mg/kg subcutaneously. Blood samples were collected at 0.5, 1, 2, 3, and 6 h, and the sera were assayed by a bioassay procedure in which *Bacillus subtilis* ATCC 6633 was used as the assay organism (2).

TABLE 3. Potency of A-61827 and ciprofloxacin in mouse protection tests

Organism	Log CFU per mouse	No. of LD_{50}[a] given	Compound	MIC (μg/ml)	ED_{50}[b] (95% confidence limits) (mg/kg per day)	
					Subcutaneous	Oral
E. coli Juhl	5.7	100	A-61827	0.03	0.4 (0.2–0.6)	1.6 (0.9–2.6)
			Ciprofloxacin	0.008	0.2 (0.1–0.3)	1.6 (1.0–2.5)
P. aeruginosa 5007	6.1	100	A-61827	0.5	6.3 (3.5–11.4)	13.3 (6.8–26.2)
			Ciprofloxacin	0.12	1.6 (1.0–2.5)	21.8 (12.3–38.5)
P. aeruginosa 5005	3.8	10	A-61827	0.5	2.1 (1.1–3.8)	3.5 (2.2–5.5)
			Ciprofloxacin	0.12	1.2 (0.8–1.8)	3.3 (1.7–6.5)
S. aureus NCTC 10649	5.3	1,000	A-61827	0.03	0.2 (0.1–0.3)	1.5 (1.1–2.0)
			Ciprofloxacin	0.25	3.7 (2.6–5.4)	10.3 (6.7–17.2)
S. pyogenes C203	2.8	100	A-61827	0.06	3.1 (1.5–6.5)	6.4 (3.1–13.1)
			Ciprofloxacin	0.25	11.4 (5.9–22.1)	99.0 (8.9–1,097.1)
S. typhimurium LT2	3.8	100	A-61827	0.03	13.6 (10.1–18.3)	20.5 (7.6–55.3)
			Ciprofloxacin	0.008	6.5 (3.8–11.2)	87.3 (8.9–854.4)

[a] LD_{50}, 50% Lethal dose.
[b] ED_{50}, 50% Effective dose.

TABLE 4. Number of viable *P. aeruginosa* in the kidneys of mice[a]

Drug dose (mg/kg)	Log CFU ± SEM in two kidneys after the following treatment:		
	A-61827	Ciprofloxacin	None (control)
0			5.6 ± 0.4
6.3	5.9 ± 0.6	6.6 ± 0.2	
25	4.0 ± 0.5	5.3 ± 0.4	
100	3.4 ± 0.7	3.7 ± 0.5	

[a] Compounds were administered orally by gavage as a single dose 24 h after infection. The MICs of A-61827 and ciprofloxacin for *P. aeruginosa* 5007 were 0.5 and 0.1 μg/ml, respectively.

TABLE 6. Pharmacokinetics of A-61827 and ciprofloxacin in mice

Compound[a]	Route of administration	C_{max}[b] (μg/ml)	$t_{1/2}$[c] (h)	AUC[d] (μg · h/ml)
A-61827	Oral	2.3	3.9	6.4
Ciprofloxacin	Oral	2.4	1.2	3.4
A-61827	s.c.	1.2	1.7	2.9
Ciprofloxacin	s.c.	2.2	1.3	3.3

[a] Compounds were administered at a dose of 100 mg/kg orally and 10 mg/kg subcutaneously (s.c.).
[b] C_{max}, peak concentration of drug in serum.
[c] $t_{1/2}$, Half-life in serum.
[d] AUC, Area under the curve for drug in serum.

RESULTS

In vitro potency of A-61827 and ciprofloxacin. The MICs of A-61827 and ciprofloxacin for a variety of aerobic and anaerobic organisms are shown in Table 1. A-61827 was generally 1 to 3 twofold dilutions less potent than ciprofloxacin against members of the family *Enterobacteriaceae* and *P. aeruginosa*. A-61827 was 2 to 3 twofold dilutions more potent against *Pseudomonas maltophilia* and 1 to 3 twofold dilutions less potent than ciprofloxacin against *Pseudomonas pseudoalcaligenes*, *Pseudomonas fluorescens*, and *Pseudomonas cepacia*. A-61827 is 1 to 2 twofold dilutions more potent than ciprofloxacin against *Branhamella catarrhalis*, *N. gonorrhoeae*, and *Enterococcus* species; 3 twofold dilutions more potent than ciprofloxacin against *S. aureus*; and 1 to 2 twofold dilutions more potent than ciprofloxacin against streptococci, *L. pneumophila*, and *Campylobacter jejuni*. Methicillin-resistant strains of *S. aureus* were as susceptible to the two quinolones as methicillin-susceptible *S. aureus* strains. Similarly, penicillin-resistant and -susceptible *N. gonorrhoeae* were equally susceptible to the quinolones. A-61827 was 3 to 4 twofold dilutions more active than ciprofloxacin against anaerobic gram-negative bacteria and 1 to 3 twofold dilutions more active than ciprofloxacin against anaerobic gram-positive bacteria, including *Clostridium difficile*.

Effect of serum on the potency of A-61827. The MICs of A-61827 were unchanged or 1 to 4 twofold dilutions higher in medium containing 50% human serum. The MICs of ciprofloxacin are 1 to ≤3 twofold dilutions higher in serum than in broth (Table 2).

Effect of urine on the potency of A-61827. The potency of A-61827 was decreased by 3 to 7 twofold dilutions when tested in urine against one strain each of *Staphylococcus epidermidis*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Proteus vulgaris*, and *Acinetobacter calcoaceticus*; two strains each of *Enterococcus faecalis* and *Klebsiella pneumoniae*; and four strains each of *E. coli* and *P. aeruginosa*. This decrease in potency was similar to or 2 twofold dilutions less than that seen when ciprofloxacin was tested in urine. The effect of urine is probably of little clinical significance because of the high concentrations achieved in urine.

Effect of pH. The MICs of A-61827 and ciprofloxacin for the same organisms tested in experiments examining the effect of urine were equal or within 1 twofold dilution at pHs 7.2 and 8.0. A-61827 had the same MICs or 1-twofold-dilution-higher MICs when tested at pHs 6.5 and 7.2, whereas ciprofloxacin was generally 2 twofold dilutions less active at pH 6.5 than at pH 7.2.

Effects of Ca^{2+} and Mg^{2+}. The MICs of A-61827 in the presence of Ca^{2+} or Mg^{2+} were unchanged or increased 1 to 2 twofold dilutions. The MICs of ciprofloxacin were increased 1 to 4 twofold dilutions in the presence of these cations.

Time-kill studies. Viable-cell counts of *E. coli* Juhl were reduced from 8.6×10^5 to 7×10^2 CFU/ml within 2 h and to 3×10^2 CFU/ml within 4 h after exposure to four times the MIC of A-61827. Viable-cell counts were reduced to $<3 \times 10^2$ CFU/ml within 2 h after exposure to eight times the MIC of A-61827. These reductions represent >99.9% within 2 h after exposure to four or eight times the MIC. The results with ciprofloxacin were similar to those for A-61827.

Frequency of resistance development. The frequencies of resistance development when selected at four times the MICs of A-61827 and ciprofloxacin were 3.4×10^{-7} and 6.7×10^{-8} for *S. aureus* CMX730A, $<1 \times 10^{-9}$ and 1.7×10^{-7} for *E. coli* Juhl, and 5.3×10^{-8} and 3.4×10^{-8} for *P. aeruginosa* 5007, respectively.

Mouse protection tests. When administered orally and subcutaneously, A-61827 was as active as ciprofloxacin against *E. coli* and *P. aeruginosa* and 5 to 10 times more active than ciprofloxacin against *S. aureus* and *Streptococcus pyogenes* (Table 3). A-61827 was as active as ciprofloxacin against *Salmonella typhimurium*.

Experimental *Pseudomonas* pyelonephritis. The activity of A-61827 was 2 twofold dilutions less than that of ciprofloxacin in vitro against the *P. aeruginosa* strain used in this infection model. However, it was as active as ciprofloxacin in reducing the numbers of viable *P. aeruginosa* in the kidneys of mice (Table 4).

Experimental *Bacteroides fragilis* abscess. The activity of A-61827 was 4 twofold dilutions more than that of ciprofloxacin in vitro against *Bacteroides fragilis* ATCC 25285 and was more than that of ciprofloxacin in the in vivo

TABLE 5. Numbers of viable *Bacteroides fragilis* isolated from abscesses[a]

Drug dose (mg/kg)	Log CFU ± SEM after the following treatment:			
	A-61827	Ciprofloxacin	Metronidazole	None (control)
0				3.4 ± 0.16
3.1	3.7 ± 0.5	4.0 ± 0.1	3.8 ± 0.2	
12.5	2.7 ± 0.5	3.6 ± 0.2	3.4 ± 0.1	
50.0	0 ± 0.0	2.4 ± 0.2	2.0 ± 0.2	

[a] The MICs of A-61827, ciprofloxacin, and metronidazole for *Bacteroides fragilis* ATCC 25285 were 0.5, 4, and 0.5 μg/ml, respectively.

abscess model (Table 5). A-61827 cleared the infection in all abscesses when treated with 50 mg/kg, whereas in ciprofloxacin-treated animals, 2.4 (±0.2) log CFU was found in the abscesses. The activity of A-61827 against *Bacteroides fragilis* was also compared with that of metronidazole (Table 5). A-61827 was at least four times as active as metronidazole in this infection model.

Pharmacokinetics in mice. The serum pharmacokinetics of A-61827 and ciprofloxacin are shown in Table 6. Although the peak concentrations of A-61827 and ciprofloxacin in serum were the same, the half-life of A-61827 in serum was three times longer than that of ciprofloxacin after oral administration.

DISCUSSION

The new fluoroquinolones have excellent activity against bacteria. However, they do not have significant activity against anaerobic bacteria. A-61827 was active against staphylococci, streptococci, enteric bacteria, *P. aeruginosa*, and anaerobes. A-61827 was more potent than ciprofloxacin against streptococci and staphylococci but 1 to 4 twofold dilutions less active than ciprofloxacin against enteric bacteria and *P. aeruginosa*. A-61827 had significant activity against anaerobic bacteria, and all anaerobes were susceptible to ≤4 μg/ml. A-61827 was similar to other fluoroquinolones in being bactericidal to logarithmically growing bacteria. The activity of A-61827 against stationary-phase cells has not been studied.

The half-life of A-61827 in serum after oral administration was better than that of ciprofloxacin. The excellent pharmacokinetic properties of A-61827 are reflected in mouse protection tests and its efficacy in the mouse pyelonephritis test. The excellent potency, broad spectrum, and good pharmacokinetics of A-61827 make this a promising candidate for clinical studies.

LITERATURE CITED

1. **Cornett, J. B., and M. P. Wentland.** 1986. Quinolone antibacterial agents. Annu. Rep. Med. Chem. **21**:139–148.
2. **Fernandes, P. B., D. T. W. Chu, R. R. Bower, K. P. Jarvis, N. R. Ramer, and N. Shipkowitz.** 1986. In vivo evaluation of A-56619 (difloxacin) and A-56620: new aryl-fluoroquinolones. Antimicrob. Agents Chemother. **29**:201–208.
3. **Fernandes, P. B., C. W. Hanson, J. M. Stamm, C. Vojtko, N. L. Shipkowitz, and E. St. Martin.** 1987. The frequency of in vitro resistance development to fluoroquinolones and the use of a murine pyelonephritis model to demonstrate selection of resistance in vivo. J. Antimicrob. Chemother. **19**:449–466.
4. **Fernandes, P. B., N. Shipkowitz, R. R. Bower, K. P. Jarvis, J. Weisz, and D. T. W. Chu.** 1986. In vitro and in vivo potency of five new fluoroquinolones against anaerobic bacteria. J. Antimicrob. Chemother. **18**:693–701.
5. **King, A., and I. Phillips.** 1986. The comparative in vitro activity of eight newer quinolones and nalidixic activity. J. Antimicrob. Chemother. **18**(Suppl. D):1–20.
6. **National Committee for Clinical Laboratory Standards.** 1985. Standard methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A. National Committee for Clinical Laboratory Standards, Villanova, Pa.
7. **National Committee for Clinical Laboratory Standards.** 1985. Reference agar dilution procedure for antimicrobial susceptibility testing of anaerobic bacteria. Approved standard M11-A. National Committee for Clinical Laboratory Standards, Villanova, Pa.
8. **Stamm, J. M., C. W. Hanson, D. T. W. Chu, R. Bailer, C. Vojtko, and P. B. Fernandes.** 1986. In vitro evaluation of A-56619 (difloxacin) and A-56620: new aryl-fluoroquinolones. Antimicrob. Agents Chemother. **29**:193–200.