In Vitro Activity of Bay y 3118, a New Quinolone

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MICs of Bay y 3118, ciprofloxacin, ofloxacin, clarithromycin, azithromycin, cefuroxime, amoxicillinclavulanate, and trimethoprim-sulfamethoxazole for 878 recent clinical isolates were determined by broth microdilution methods. Among the three quinolones, Bay y 3118 was the most active against *Haemophilus influenzae*, *Moraxella catarrhalis*, *Acinetobacter baumannii*, *Xanthomonas maltophilia*, gram-positive cocci, and anaerobes; MICs for 50% of the strains (MIC₅₀s) and MIC₉₀s were ≤ 0.015 and ≤ 0.015 , ≤ 0.015 and ≤ 0.015 , 0.03 and 2, 0.25 and 0.5, 0.06 and 1, and 0.12 and 0.25 µg/ml, respectively. For gram-positive cocci and anaerobes, these values were 16- to 32-fold (4 to 5 log₂ dilution steps) lower than those for ciprofloxacin and ofloxacin. Bay y 3118 was similar in activity to ciprofloxacin and more active than ofloxacin against members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa*; Bay y 3118 MIC₅₀s and MIC₉₀s were 0.03 and 0.25 and 0.5 and 8 µg/ml, respectively. Scattergrams and regression analyses comparing quinolone MICs indicated that, despite differences in activity, organisms relatively susceptible to one were relatively susceptible to all and organisms relatively resistant to one were relatively resistant to all. However, the greater in vitro activity of Bay y 3118 was most pronounced against relatively resistant organisms. Pending pharmacokinetic and safety data for Bay y 3118, there is reasonable anticipation that its enhanced activity against gram-positive cocci and anaerobes would broaden the clinical utility of the quinolone class of antimicrobial agents.

Bay y 3118 is a new 6-fluoro-1-piperazinyl-quinolone similar in structure to ciprofloxacin but with a chloride at the 8 position and a bicyclic substituent at the 7 position of the 3-quinoline carboxylic acid nucleus (2, 12). In this study, the MICs of Bay y 3118, ciprofloxacin, ofloxacin, clarithromycin, azithromycin, cefuroxime, amoxicillin-clavulanate, and trimethoprim-sulfamethoxazole (TMP-SMZ) for 878 recent clinical isolates were determined by broth microdilution methods. Scattergrams and regression analyses were used to compare in vitro activities and describe cross-susceptibility and cross-resistance among the quinolones.

MATERIALS AND METHODS

Organisms. The organisms studied included 878 bacterial strains arbitrarily selected from isolates at the Ohio State University Hospitals. Most were fresh clinical isolates collected during the course of the study, November 1992 through January 1993. For infrequently isolated species, some strains collected during the past several years and stored at -70° C were used. Duplicate isolates from the same patients were excluded.

Antimicrobial agents. Bay y 3118 and ciprofloxacin were obtained from Miles Inc., West Haven, Conn.; ofloxacin was obtained from R. W. Johnson Pharmaceutical Research Institute, Raritan, N.J.; clarithromycin was obtained from Abbott Laboratories, Abbott Park, Ill.; azithromycin was obtained from Pfizer Inc., Groton, Conn.; cefuroxime was obtained from Eli Lilly and Co., Indianapolis, Ind., amoxicillin-clavulanate was obtained from Beecham Laboratories, Bristol, Tenn.; and TMP-SMZ was obtained from Hoffmann-LaRoche Inc., Nutley, N.J.

Laboratory standard powders were diluted in accordance with manufacturers' recommendations and dispensed into microdilution plates by using an MIC-2000 dispensing machine (Dynatech Laboratories, Inc., Chantilly, Va.) in \log_2 dilution steps from 0.015 to 32 µg/ml (0.015 to 8 µg of TMP per ml for TMP-SMZ). Plates were stored at -70° C until used.

Susceptibility tests. MICs for nonfastidious organisms and Haemophilus influenzae were determined by a standardized microdilution method (8) in 0.1-ml volumes of cation-adjusted Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) and haemophilus test medium, respectively. For Streptococcus pyogenes, Streptococcus pneumoniae, and the viridans group streptococci, haemophilus test medium was also used; incubation was in room air for approximately 20 h. For anaerobes, the medium was Schaedler broth (Difco) supplemented with 1% heat-inactivated horse serum and 0.5 μ g of vitamin K₁ per ml; incubation was in 85% N_2 -10% H_2 -5% CO₂ for approximately 48 h. Microdilution plates were inoculated with disposable inoculators (Dynatech) so that the final inoculum was approximately $5 \times$ 10^5 CFU/ml. Recommended control strains (8) were used. MIC breakpoints for defining susceptibility, intermediate susceptibility, and resistance for marketed drugs were those recommended by manufacturers and the National Committee for Clinical Laboratory Standards (9).

Scattergrams and regression analyses. MICs were entered into a Macintosh IIci computer by using File Maker Pro software. Quinolone MICs were converted to \log_2 values and then exported for subsequent analysis. Scattergrams comparing Bay y 3118 MICs and, for comparison, ofloxacin MICs with ciprofloxacin MICs were plotted with Cricket Graph III. For regression analyses, lines of best fit were calculated. r^2 , the coefficient of determination, indicated the proportion of the total variance in y which could be explained by the variance in x. For example, if r^2 was 0.85, 85% of the total variance in the MIC of drug Y would be determined by the MIC of drug X.

Range 398 989 Haemophikus influenzae AS* (18) Bay y 3118 ≤0.015	Organism (no. of strains)	Drug	MIC (µg/ml)		
Ciprofloxacin c0.015-0.03 c0.015 0.00 Ofloxacin 0.03-0.12 0.06 0.0 Arithomycin 1.16 8 16 Arithomycin 0.25.4 1 2 Catinoxine 0.25.1 1 4 Marithomycin 0.25.4 1 4 TMP-SMZ 0.06 ->8 0.05 \$ 0.015 \$ 0.015 \$ 0.015 \$ \$ 0.015 \$ \$ 0.05 \$ <	organism (no. or stranis)	Diug	Range	50%	90%
Ciprofloxacin c0.015 0.03 c0.015 0.00 Odloxacin 0.03-0.12 0.06 0.0 Arithromycin 0.254 1 2 Cefuroxine 0.254 1 4 AmoxClav 0.25-4 1 4 AmoxClav 0.25-4 0.06 0.5 Haemophilus influenzae AR* (21) Bay y 3118 <0.015	Haemophilus influenzae AS ^a (18)	Bay y 3118	≤0.015	≤0.015	≤0.01
$\begin{array}{c cccc} Clarithromycin & 1-16 & 8 & 16 \\ Azithromycin & 0.25.4 & 1 & 4 \\ Amox-Clav^* & 0.25.4 & 1 & 4 \\ Cefuroxine & 0.45.4 & 0.06 & 0.5 \\ Ciprofloxacin & 0.0015.0.03 & 50.015 & 50.0 \\ Ciprofloxacin & 0.0015.0.03 & 50.015 & 50.0 \\ Ciprofloxacin & 0.03-0.06 & 0.03 & 0.0 \\ Ciprofloxacin & 0.5-2 & 1 & 2 \\ Azithromycin & 0.5-2 & 1 & 2 \\ Ciprofloxacin & 0.015.0.03 & 50.015 & 50.0 \\ Ciprofloxacin & 0.006-0.12 & 0.06 & 0.1 \\ Ciprofloxacin & 0.06-0.12 & 0.06 & 0.1 \\ Amox-Clav & 0.06-0.12 & 0.06 & 0.1 \\ Amox-Clav & 0.06-0.12 & 0.06 & 0.1 \\ Amox-Clav & 0.06-0.12 & 0.05 & 0.1 \\ Ciprofloxacin & 0.06-0.12 & 0.10 & 0.0 \\ Ciprofloxacin & 0.005-0.015 & 50.0 \\ Ciprofloxacin & 0.03-0.05 & 0.12 & 0.2 \\ Azithromycin & 0.06-0.2 & 0.12 & 0.1 \\ Amox-Clav & 0.06-0.12 & 0.16 & 0.03 & 0.0 \\ Ciprofloxacin & 0.03-0.03 & 0.015 & 50.0 \\ Ciprofloxacin & 0.03-0.1 & 0.00 & 0.1 \\ Ceturoxime & 0.5-2 & 2 & 2 & 2 \\ Ceturoxime & 0.5-2 & 0.2 & 0.2 & 0.12 & 0.2 \\ Ceturoxime & 0.5-2 & 0.2 & 0.2 & 0.015 & 0.0 \\ Ciprofloxacin & 0.03-0.03 & 0.015 & 50.0 \\ Ciprofloxacin & 0.03-0.03 & 0.015 & 50.0 \\ Ciprofloxacin & 0.03-0.1 & 0.03 & 0.0 \\ Ciprofloxacin & 0.03-0.1 & 0.03 & 0.0 \\ Ciprofloxacin & 0.03-0.1 & 0.03 & 0.0 \\ Ciprofloxacin & 0.03-0.5 & 0.015 & 0.0 \\ Ciprofloxacin & 0.03-0.0 & 0.02 & 0.015 &$			≤0.015–0.03	≤0.015	0.03
Azithomycin $0.25.4$ 1 2 Ceturoxine $0.25.1$ 0.5 1 TMP-SMZ $0.6->8$ 0.06 0.5 Jacon Colar $0.05.21$ 0.5 1 Jacon Colar $0.05.21$ 0.5 1 Jacon Colar $0.015.0.03$ 50.015 50.0 Ciprofloxacin $<0.03-0.06$ 0.03 0.015 Amox Clav $0.5-2$ 1 2 Catultromycin $0.5-2$ 1 2 Amox-Clav $0.5-1$ 1 1 Jacon Clav $0.05-0.3$ 0.015 0.06 Catultromycin $0.5-2$ 1 2 Amox-Clav $0.5-1$ 1 1 Jacon Clav $0.05-0.15$ 50.015 50.015 Catultromycin $0.06-0.12$ 0.06 0.1 Arithomycin $0.06-0.12$ 0.06 0.1 Arithomycin $0.06-0.5$ 0.25 0.5 Arithomycin $0.06-0.5$ 0.25 0.5 Arithomycin 0.06		Ofloxacin	0.03-0.12	0.06	0.06
$ \begin{array}{c} \mbox{Celaroxine} & 0.25.4 & 1 & 4 \\ \mbox{Amox-Clav} & 0.25.1 & 0.6 & 0.5 \\ Imposed of the second o$		Clarithromycin	1–16	8	16
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		Azithromycin	0.25-4	1	2
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Jaemophilus influenzae AR* (21) Bay y 3118 < 0.015 ≤ 0.015		Amox-Clav ^b	0.25-1	0.5	1
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Ciprofloxacin ≤0.015-0.03 ≤0.015 0.03 0.00 Offoxacin 0.03-0.06 0.03 0.0 Clarithromycin 1-16 8 8 Authromycin 0.5-2 1 2 Cefuroxime 0.5-8 1 2 AmoxClav 0.5-1 1 1 Moraxella catarrhalis AS (5) Bay y 3118 ≤0.015 ≤0.015 ≤0.015 Ciprofloxacin 0.06-0.12 0.06 0.03 0.0 Offoxacin 0.06-0.12 0.06 0.1 2.0.2 Azithromycin 0.06-0.12 0.06 0.1 2.0.2 Azithromycin 0.06-0.12 0.06 0.1 2.0.2 Azithromycin 0.06-0.12 0.12 0.1 Anox-Clav 0.06-0.12 0.12 0.1 Offoxacin 0.06-0.5 0.12 0.12 0.1 Ciprofloxacin 0.03-0.25 0.12 0.2 0.12 0.1 Cathroronycin 0.05-0.5 0.12	Jaemophilus influenzae AR ^a (21)	Bay y 3118	≤0.015	≤0.015	≤0.015
$ \begin{array}{c cccc} Clarithromycin & 1-16 & 8 & 8 & 8 \\ Azithromycin & 0.5-2 & 1 & 2 \\ Cefuroxine & 0.5-8 & 1 & 1 & 1 \\ TMP-SMZ & 0.03-2 & 0.06 & 0.2 \\ \hline Amox.Clav & 0.5-1 & 1 & 1 & 1 \\ TMP-SMZ & 0.03-2 & 0.06 & 0.2 \\ \hline Amox.Clav & 0.5-1 & 0.15 & \pm 0.015 & \pm 0.01$	•••		≤0.015–0.03	≤0.015	≤0.015
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$ \begin{array}{c ccc} Cefuroxime & 0.5-8 & 1 & 2 \\ Amox.Clav & 0.5-1 & 1 & 1 \\ TMP-SMZ & 0.03-2 & 0.06 & 0.2 \\ \hline \mbox{foraxella catarrhalis AS (5)} & Bay y 3118 & $ 0.015 & $ 0.015 & $ 0.015 & $ 0.015 & $ 0.015 & $ 0.015 & $ 0.015 & $ 0.015 & $ 0.015 & $ 0.015 & $ 0.015 & $ 0.015 & $ 0.016 & $ 0.016 & $ 0.016 & $ 0.016 & $ 0.016 & $ 0.016 & $ 0.016 & $ 0.016 & $ 0.016 & $ 0.016 & $ 0.012 & 0.06 & $ 0.11 & $ 0.06 & 0.12 & $ 0.06 & $ 0.12 & $ 0.05 & $ 0.015 & $ 0$		Clarithromycin	1–16	8	8
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Ciprofioxacin c0.015-0.03 0.03 0.03 Oftoxacin 0.06-0.12 0.06 0.1 Clarithromycin 0.06-0.12 0.06 0.1 Azithromycin 0.06-0.12 0.06 0.1 Cefurozine 0.25-1 0.5 1 Amox-Clav 0.06-0.12 0.06 0.1 TMP-SMZ 0.06-0.5 0.25 0.5 Moraxella catarrhalis AR (20) Bay y 3118 <0.015	foraxella catarrhalis AS (5)	Bay v 3118	<0.015	<0.015	≤0.015
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$ \begin{array}{cccc} Cefuroxime & 0.5-2 & 2 & 2 \\ Amox-Clav & 0.03-0.5 & 0.12 & 0.2 \\ TMP-SMZ & 0.12-1 & 0.25 & 0.5 \\ \hline \text{TMP-SMZ} & 0.12-1 & 0.25 & 0.5 \\ \hline \text{Scherichia coli (30)} & Bay y 3118 & \leq 0.015-0.03 & \leq 0.015 & \leq 0.0 \\ Ciprofloxacin & 0.03-0.12 & 0.06 & 0.1 \\ Cefuroxime & 0.5-16 & 4 & 8 \\ Amox-Clav & 1->32 & 8 & 16 \\ TMP-SMZ & 0.03->8 & 0.12 & 0.2 \\ \hline \text{Ciprofloxacin } & \leq 0.015-0.25 & 0.03 & 0.2 \\ Ciprofloxacin & 0.12-2 & 0.12 & 1 \\ Cefuroxime & 2-8 & 4 & 8 \\ Amox-Clav & 2-8 & 4 & 8 \\ TMP-SMZ & 0.06->8 & 0.25 & 1 \\ \hline \text{Ciprofloxacin } & \leq 0.015-0.25 & 0.03 & 0.0 \\ Ciprofloxacin & 0.12-2 & 0.12 & 1 \\ Cefuroxime & 2-8 & 4 & 8 \\ TMP-SMZ & 0.06->8 & 0.25 & 1 \\ \hline \text{Ciprofloxacin } & \leq 0.015-0.25 & 0.03 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.5 & \leq 0.015 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.5 & \leq 0.015 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.5 & \leq 0.015 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.5 & \leq 0.015 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.5 & \leq 0.015 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.5 & \leq 0.015 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.5 & \leq 0.015 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.25 & 0.03 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.25 & 0.03 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.25 & 0.03 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.25 & 0.03 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.03 & \leq 0.015 & 0.0 \\ Ofloxacin & 0.06-1 & 0.12 & 0.2 \\ Cefuroxime & 1-32 & 4 & 8 \\ Amox-Clav & 2-8 & 4 & 4 \\ TMP-SMZ & 0.06-0.25 & 0.12 & 0.2 \\ Ciprofloxacin & \leq 0.015-0.03 & \leq 0.015 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.03 & \leq 0.015 & 0.0 \\ Ciprofloxacin & \leq 0.015-0.03 & \leq 0.015 & 0.0 \\ Ciprofloxacin & 0.06-0.12 & 0.06 & 0.1 \\ Cefuroxime & 2-8 & 4 & 8 \\ Amox-Clav & 1-4 & 2 & 4 \\ \end{array}$					
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$Citrobacter diversus (19) \begin{array}{c cccc} Ofioxacin & 0.12-2 & 0.12 & 1 \\ Cefuroxime & 2-8 & 4 & 8 \\ Amox-Clav & 2-8 & 4 & 8 \\ TMP-SMZ & 0.06->8 & 0.25 & 1 \end{array}$	seosiena pricarionae (25)				
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$\begin{array}{c ccccc} Amox-Clav & 2-8 & 4 & 4 \\ TMP-SMZ & 0.06-0.25 & 0.12 & 0.2 \\ \hline Citrobacter diversus (19) & Bay y 3118 & \leq 0.015-0.03 & \leq 0.015 & \leq 0.00 \\ Ciprofloxacin & \leq 0.015-0.03 & \leq 0.015 & 0.00 \\ Ofloxacin & 0.06-0.12 & 0.06 & 0.11 \\ Cefuroxime & 2-8 & 4 & 8 \\ Amox-Clav & 1-4 & 2 & 4 \\ \hline \end{array}$					
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Ciprofloxacin $\leq 0.015-0.03$ ≤ 0.015 0.0 Ofloxacin $0.06-0.12$ 0.06 0.11 Cefuroxime $2-8$ 48Amox-Clav $1-4$ 24	Citrobacter diversus (19)	Bay v 3118	≤0.015-0.03	≤0.015	≤0.015
Ofioxacin 0.06–0.12 0.06 0.11 Cefuroxime 2–8 4 8 Amox-Clay 1–4 2 4					0.03
Cefuroxime 2-8 4 8 Amox-Clav 1-4 2 4					0.03
Amox-Clav 1-4 2 4					
		TMP-SMZ	0.06-0.25	0.12	0.25

TABLE 1. In vitro activities of Bay y 3118 and comparative antimicrobial agents

Organism (no. of strains)	Drug	MIC (µg/ml)			
organism (no. or strains)	Diug	Range	50%	90%	
Citrobacter freundii (20)	Bay y 3118	≤0.015-1	0.06	0.25	
	Ciprofloxacin	≤0.015–0.5	0.03	0.25	
	Ofloxacin	0.06-4	0.12	0.5	
	TMP-SMZ	0.06->8	0.12	>8	
Enterobacter aerogenes (20)	Bay y 3118	≤0.015–0.25	0.03	0.06	
	Ciprofloxacin	≤0.015–2	0.03	0.06	
	Ofloxacin	0.06-4	0.12	0.25	
	TMP-SMZ	0.06->8	0.25	0.25	
Enterobacter cloacae (20)	Bay y 3118	≤0.015-0.25	≤0.015	0.12	
	Ciprofloxacin	≤0.015–1	≤0.015	0.06	
	Ofloxacin	0.03-4	0.12	0.5	
	TMP-SMZ	0.06->8	0.25	0.5	
Serratia marcescens (20)	Bay y 3118	0.06–1	0.25	0.5	
	Ciprofloxacin	0.06-1	0.25	0.5	
	Ofloxacin	0.25-4	0.5	2	
	TMP-SMZ	0.25-4	0.5	2	
Proteus mirabilis (20)	Bay y 3118	0.03-4	0.06	0.12	
ζ, γ	Ciprofloxacin	≤0.015	0.03	0.06	
	Ofloxacin	0.06-32	0.12	0.25	
	Cefuroxime	0.5-8	1	2	
	Amox-Clav	0.5-32	1	2	
	TMP-SMZ	0.12->8	0.25	0.25	
Proteus vulgaris (19)	Bay y 3118	0.03-0.5	0.06	0.25	
	Ciprofloxacin	≤0.015–0.5	0.03	0.06	
	Ofloxacin	0.06-2	0.12	0.25	
	Amox-Clav TMP-SMZ	4->32 0.12-0.5	8 0.25	>32 0.5	
1(D 4110				
Morganella morganii (20)	Bay y 3118	≤0.015-0.12	0.03	0.06	
	Ciprofloxacin Ofloxacin	≤0.015–0.12 0.06–0.25	≤0.015 0.12	0.03 0.12	
	TMP-SMZ	0.12->8	0.25	0.12	
Providencia stuartii (19)	Bay y 3118	0.03-4	0.06	2	
rovuencu siuurii (19)	Ciprofloxacin	0.03 - 32	0.06	2 32	
	Ofloxacin	0.12->32	0.25	16	
	Cefuroxime	0.5->32	8	>32	
	TMP-SMZ	0.25->8	4	>8	
Pseudomonas aeruginosa (30)	Bay y 3118	0.25->32	0.5	8	
0	Ciprofloxacin	0.06->32	0.25	32	
	Ofloxacin	0.5->32	2	>32	
Xanthomonas maltophilia (20)	Bay y 3118	0.06-8	0.25	0.5	
	Ciprofloxacin	1-32	2	8	
	Ofloxacin	1–32	2	8	
	TMP-SMZ	0.25–2	0.5	0.5	
Acinetobacter baumannii (20)	Bay y 3118	≤0.015–8	0.03	2	
	Ciprofloxacin	0.12->32	0.25	>32	
	Ofloxacin	0.25->32	0.5	16	
	TMP-SMZ	0.03->8	0.25	>8	
Staphylococcus aureus MS ^d (25)	Bay y 3118	≤0.015–0.03	≤0.015	0.03	
	Ciprofloxacin	0.06-1	0.5	1	
	Ofloxacin Clarithromycin	0.12–1 0.25–>32	0.5 0.25	1 >32	
	Azithromycin	0.25->32	0.25	>32	
	Cefuroxime	2-4	2	- 32	
	Amox-Clav	0.25-2	1	2	
	TMP-SMZ	0.06-1	0.12	0.12	

TABLE 1-Continued

Organism (no. of strains)	Drug	MIC (µg/ml)		
	5105	Range	50%	90%
Staphylococcus aureus MR ^d (30)	Bay y 3118	0.03-4	0.5	1
	Ciprofloxacin	0.5->32	32	>32
	Ofloxacin	0.5->32	16	>32
	Clarithromycin	0.25->32	>32	>32
	Azithromycin	0.5->32	>32	>32
	TMP-SMŽ	0.06–>8	0.12	>8
Staphylococcus epidermidis MS (20)	Bay y 3118	≤0.015–0.03	0.03	0.03
	Ciprofloxacin	0.12-0.5	0.25	0.25
	Ofloxacin	0.25-1	0.5	0.5
	Clarithromycin	0.12->32	0.25	>32
	Azithromycin	0.25->32	0.5	>32
	Cefuroxime	0.03-1	0.5	0.5
	Amox-Clav	0.06-0.5	0.25	0.5
	TMP-SMZ	0.06-4	0.25	0.5
Staphylococcus epidermidis MR (20)	Bay y 3118	0.03-1	0.06	0.5
	Ciprofloxacin	0.25->32	1	>32
	Ofloxacin	0.5->32	1	16
	Clarithromycin	0.25->32	>32	>32
	Azithromycin	0.25->32	>32	>32
	TMP-SMŽ	0.12-8	0.25	4
Staphylococcus haemolyticus MS (20)	Bay y 3118	≤0.015–0.03	0.03	0.03
	Ciprofloxacin	0.12-0.5	0.25	0.25
	Ofloxacin	0.25-1	0.25	0.5
	Clarithromycin	0.25->32	0.5	>32
	Azithromycin	1->32	4	>32
	Cefuroxime	0.5-8	2	2
	Amox-Clav	0.12-2	0.5	0.5
	TMP-SMZ	0.06->8	0.25	0.25
Staphylococcus haemolyticus MR (25)	Bay y 3118	≤0.015–2	0.5	1
	Ciprofloxacin	0.12->32	32	>32
	Ofloxacin	0.25->32	32	>32
	Clarithromycin	0.25->32	>32	>32
	Azithromycin	1->32	>32	>32
	TMP-SMZ	0.25->8	>8	>8
Staphylococcus hominis MS (10)	Bay y 3118	≤0.015–0.06	0.03	0.06
•••	Ciprofloxacin	0.12-0.5	0.25	0.25
	Ofloxacin	0.25-1	0.25	0.25
	Clarithromycin	0.25->32	0.25	>32
	Azithromycin	0.25->32	1	>32
	Cefuroxime	0.25–1	0.5	1
	Amox-Clav	0.12-0.5	0.25	0.25
	TMP-SMZ	0.06–1	0.25	0.25
Staphylococcus hominis MR (10)	Bay y 3118	≤0.015–1	0.03	0.5
	Ciprofloxacin	0.25->32	0.25	>32
	Ofloxacin	0.25-32	0.25	32
	Clarithromycin	0.25->32	>32	>32
	Azithromycin	0.25->32	32	>32
	TMP-SMZ	0.12->8	0.5	>8
Staphylococcus saprophyticus (20)	Bay y 3118	0.06-0.12	0.06	0.06
	Ciprofloxacin	0.5	0.5	0.5
	Ofloxacin	1-2	1	2
	Clarithromycin	0.05->32	0.5	1
	Azithromycin	2->32	4	4
	Cefuroxime	2-8	4	4
	Amox-Clav	0.5-1	0.5	1
	TMP-SMZ	0.06-0.12	0.12	0.12

TABLE 1-Continued

Organism (no. of strains)	Drug		MIC (µg/ml)	
	Diug	Range	50%	90%
Streptococcus pyogenes (20)	Bay y 3118	≤0.015–0.06	0.03	0.06
	Ciprofloxacin	0.25-4	0.5	0.5
	Ofloxacin	0.5-4	1	1
	Clarithromycin	0.03-0.06	0.03	0.06
	Azithromycin	0.25	0.25	0.25
	Cefuroxime	≤0.015–0.03	≤0.015	≤0.01
	Amox-Clav	≤0.015-0.03	≤0.015	≤0.015
	TMP-SMZ	0.12–1	0.25	0.5
Streptococcus pneumoniae (35)	Bay y 3118	≤0.015–0.5	0.06	0.06
	Ciprofloxacin	0.5->32	2	4
	Ofloxacin	0.5-32	2	2
	Clarithromycin	≤0.015-8	0.06	0.06
	Azithromycin	0.12-8	0.25	0.25
	Cefuroxime	≤0.015-4	0.03	0.25
	Amox-Clav	≤0.015-0.5	≤0.015	0.03
	TMP-SMZ	0.25->8	1	4
Streptococcus agalactiae (24)	Bay y 3118	0.03-0.5	0.06	0.06
	Ciprofloxacin	0.5–32	0.5	1
	Ofloxacin	1->32	2	2
	Clarithromycin	0.06–2	0.25	0.25
	Azithromycin	0.06–16	0.25	0.5
	Cefuroxime	≤0.015–0.06	0.06	0.06
	Amox-Clav	0.03-0.12	0.06	0.12
	TMP-SMZ	0.06-0.25	0.12	0.25
Streptococcus bovis (19)	Bay y 3118	0.03-0.12	0.06	0.12
	Ciprofloxacin	0.25–16	2	4
	Ofloxacin	1–8	4	4
	Clarithromycin	0.06->32	0.25	>32
	Azithromycin	0.12->32	0.25	>32
	Cefuroxime	0.06-0.5	0.12	0.25
	Amox-Clav	0.03-0.12	0.06	0.12
	TMP-SMZ	0.25–4	0.25	1
Viridans group streptococci (17)	Bay y 3118	0.03-0.12	0.06	0.12
	Ciprofloxacin	0.5-8	4	8
	Ofloxacin	0.5-8	4	4
	Clarithromycin	0.03-4	0.06	1
	Azithromycin	0.06–16	0.25	4
	Cefuroxime	0.06–1	0.5	0.5
	Amox-Clav	≤0.015–1	0.06	0.25
	TMP-SMZ	0.03->8	1	8
Enterococcus faecalis (20)	Bay y 3118	0.12–2	0.25	2
• • • •	Ciprofloxacin	1->32	1	>32
	Ofloxacin	2->32	4	>32
	Clarithromycin	0.5->32	>32	>32
	Azithromycin	2->32	>32	>32
	Amox-Clav	1	1	1
	TMP-SMZ	0.06->8	0.25	>8
Enterococcus faecium (20)	Bay y 3118	0.06-8	1	4
	Ciprofloxacin	0.05->32	4	>32
	Ofloxacin	2->32	8	>32
	Clarithromycin	0.5->32	>32	>32
	Azithromycin	2->32	>32	>32
	Amox-Clav	0.5->32	16	>32
	TMP-SMZ	0.03->8	0.25	>8
Enterococcus avium (16)	Bay y 3118	0.06-0.25	0.12	0.25
	Ciprofloxacin	0.5–1	1	1
	Ofloxacin	2–4	4	4
	Clarithromycin	0.06->32	0.25	>32
	Azithromycin	0.12->32	1	>32
	Amox-Clav	0.05-2	0.5	1
	TMP-SMZ	0.03-0.25	0.06	0.12

TABLE 1-Continued

Organism (no. of strains)	Drug	Drug		MIC (µg/ml)	
	Drug	Range	50%	90%	
Enterococcus durans (17)	Bay y 3118	0.03–2	0.5	1	
	Ciprofloxacin	0.25-8	2	4	
	Ofloxacin	1–16	4	8	
	Clarithromycin	0.12->32	4	>32	
	Azithromycin	0.25->32	32	>32	
	Amox-Clav	0.25-4	2	4	
	TMP-SMZ	0.12–1	0.5	1	
Bacteroides fragilis (20)	Bay y 3118	0.03-0.5	0.12	0.12	
	Ciprofloxacin	2->32	4	8	
	Ofloxacin	2–32	4	8	
	Clarithromycin	0.25->32	1	>32	
	Azithromycin	0.5->32	8	>32	
	Cefuroxime	8->32	>32	>32	
	Amox-Clav	0.5-2	0.5	2	
Bacteroides thetaiotaomicron (22)	Bay y 3118	0.06–1	0.25	0.5	
()	Ciprofloxacin	4–32	8	32	
	Ofloxacin	4-16	8	16	
	Clarithromycin	0.5->32	2	4	
	Azithromycin	1->32	8	>32	
	Cefuroxime	8->32	>32	>32	
	Amox-Clav	0.5-4	1	2	
Bacteroides melaninogenicus (9)	Bay y 3118	≤0.015–0.12	0.12	0.12	
	Ciprofloxacin	0.12-2		•••==	
	Ofloxacin	0.5-4			
	Clarithromycin	0.03-0.5			
	Azithromycin	0.06-0.5			
	Cefuroxime	≤0.015–32			
	Amox-Clav	≤0.015-0.5			
Peptostreptococcus species (30)	Bay y 3118	≤0.015–0.5	0.03	0.25	
	Ciprofloxacin	0.12-8	1	4	
	Ofloxacin	0.25-32	2	8	
	Clarithromycin	0.06->32	0.5	2	
	Azithromycin	0.25->32	1	2 4	
	Cefuroxime	0.06->32	0.5	8	
	Amox-Clav	≤0.015–16	0.25	2	
Clostridium perfringens (21)	Bay y 3118	0.03-0.25	0.12	0.25	
	Ciprofloxacin	0.25-4	0.5	1	
	Ofloxacin	0.5-4	0.5	ī	
	Clarithromycin	0.25->32	1	2	
	Azithromycin	0.25->32	2	4	
	Cefuroxime	0.25-4	4	4	
	Amox-Clav	≤0.015–0.25	0.12	0.25	
Fusobacterium species (22)	Bay y 3118	≤0.015–0.5	0.12	0.25	
()	Ciprofloxacin	0.5-8	1	2	
	Ofloxacin	0.5-8	$\frac{1}{2}$	4	
	Clarithromycin	0.5->32	2	>32	
	Azithromycin	≤0.015–16	0.25	8	
	Cefuroxime	0.03-1	0.12	0.5	
	Amox-Clav	≤0.015->32	0.12	1	

TABLE 1-Continued

^a AS, ampicillin susceptible; AR, ampicillin resistant.
^b Amox-Clav, amoxicillin-clavulanate.
^c TMP-SMZ is reported as the concentration of trimethoprim.
^d MS, methicillin susceptible; MR, methicillin resistant.

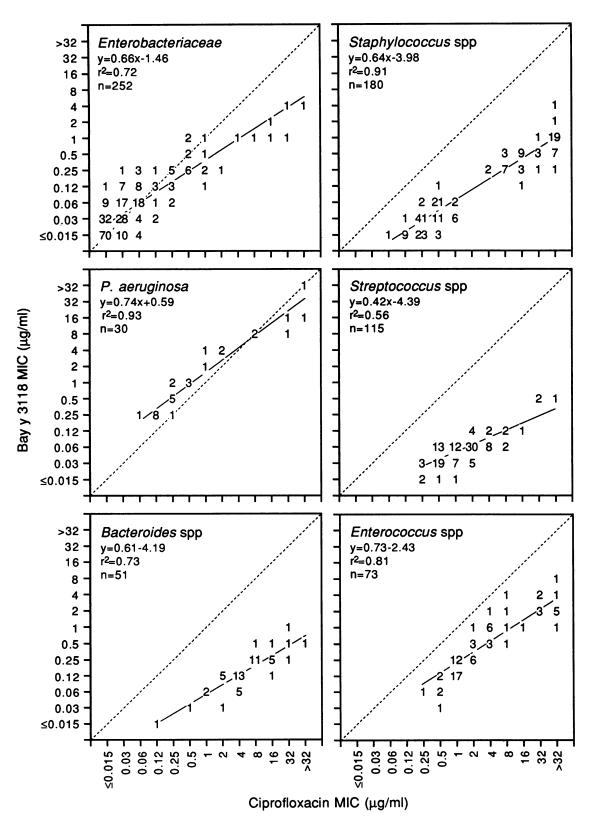


FIG. 1. Scattergrams and regression analyses comparing MICs of Bay y 3118 with MICs of ciprofloxacin. Solid lines are the lines of best fit, and dashed lines are the lines of identity.

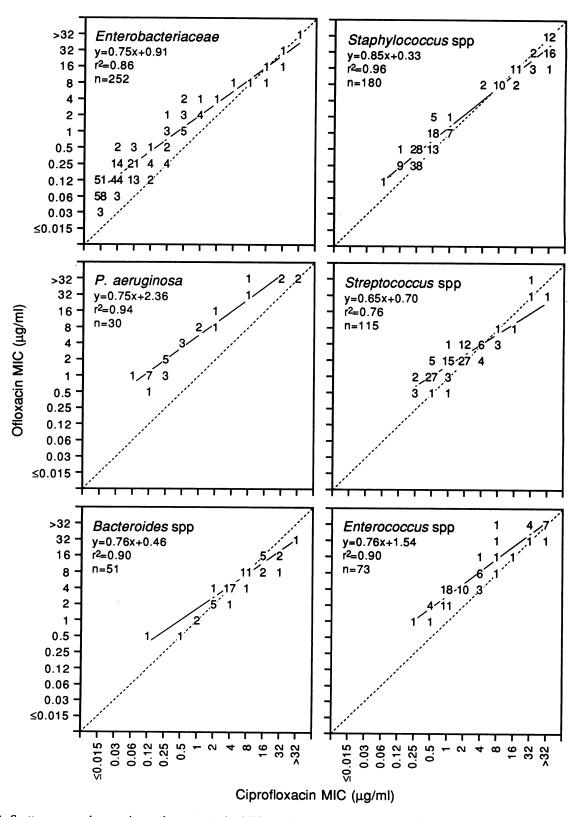


FIG. 2. Scattergrams and regression analyses comparing MICs of ofloxacin with MICs of ciprofloxacin. Solid lines are the lines of best fit, and dashed lines are the lines of identity.

RESULTS

The MICs of the eight study drugs for the 878 isolates tested are shown in Table 1. Among the three quinolones, Bay y 3118 was most active against H. influenzae, Moraxella catarrhalis, Acinetobacter baumannii, Xanthomonas maltophilia, gram-positive cocci, and anaerobes; respective MIC_{50} s and MIC_{90} s for Bay y 3118 were ≤ 0.015 and ≤ 0.015 , ≤ 0.015 and ≤ 0.015 , 0.03 and 2, 0.25 and 0.5, 0.06 and 1, and 0.12 and 0.25 µg/ml. H. influenzae and M. catarrhalis were susceptible to all study drugs. Among the staphylococci, methicillin-resistant strains were relatively quinolone resistant; Bay y 3118 MIC₉₀s for methicillin-susceptible staphylococci were $\leq 0.06 \ \mu g/ml$, and for methicillin-resistant staphylococci they were $\leq 1 \mu g/ml$. Among the enterococci, Enterococcus faecium was relatively quinolone resistant. Bay y 3118 was comparable to ciprofloxacin and more active than ofloxacin against members of the family Enterobacteriaceae and Pseudomonas aeruginosa; Bay y 3118 MIC₅₀s and MIC₉₀s were 0.03 and 0.25 and 0.5 and 8 μ g/ml, respectively. Among the Enterobacteriaceae, Providencia stuartii was relatively quinolone resistant.

Scattergrams and regression analyses comparing MICs of Bay y 3118 and ofloxacin with MICs of ciprofloxacin for six organisms and groups of organisms are shown in Fig. 1 and 2, respectively. For the aerobic organisms, there were bimodal distributions of MICs, whereas with Bacteroides spp., there was a unimodal distribution of MICs. Organisms relatively susceptible to one quinolone were relatively susceptible to the other two, and organisms relatively resistant to one were relatively resistant to the others. Figure 1 shows that Bay y 3118 was more active than ciprofloxacin against gram-positive cocci and bacteroids and similar in activity against Enterobacteriaceae and P. aeruginosa. The greater in vitro activity of Bay y 3118 was most pronounced against relatively resistant organisms. It was approximately 64-fold $(6 \log_2 \text{ dilution steps})$ more active than ciprofloxacin against ciprofloxacin-resistant staphylococci, streptococci, and bacteroids. Figure 2 shows that ofloxacin was less active than ciprofloxacin against gram-negative organisms and enterococci; for strains relatively susceptible to both drugs, the difference was approximately two- to eightfold (1 to $3 \log_2$ dilution steps). Ofloxacin was similar to ciprofloxacin in activity against staphylococci, streptococci, and bacteroids.

Bay y 3118 MICs for control strains in cation-adjusted Mueller-Hinton broth were as follows: Escherichia coli ATCC 25922, $\leq 0.015 \ \mu g/ml \ (n = 17)$; P. aeruginosa ATCC 27853, 0.25 to 0.5 $\mu g/ml \ (n = 12)$; Staphylococcus aureus ATCC 29213, $\leq 0.015 \ \mu g/ml \ (n = 13)$; and Enterococcus faecalis ATCC 29212, 0.06 to 0.12 $\mu g/ml \ (n = 13)$. In haemophilus test medium, they were as follows: S. pneumoniae ATCC 49619, 0.03 to 0.06 $\mu g/ml \ (n = 3)$ and H. influenzae ATCC 49247, $\leq 0.015 \ \mu g/ml \ (n = 4)$. In supplemented Schaedler broth, the MIC for Bacteroides fragilis ATCC 25285 was 0.06 $\mu g/ml \ (n = 4)$.

DISCUSSION

In this study, the in vitro activity of Bay y 3118 was similar to that reported for studies in the United Kingdom and Germany utilizing agar dilution methods (2, 12). Compared with ciprofloxacin and ofloxacin, it was the most active quinolone against *H. influenzae*, *M. catarrhalis*, *A. baumannii*, *X. maltophilia*, gram-positive cocci, and anaerobes. For gram-positive cocci and anaerobes, MIC₅₀s and MIC₉₀s were 16- to 32-fold (4 to 5 \log_2 dilution steps) lower than the respective values for ciprofloxacin and ofloxacin. Bay y 3118 was comparable in activity to ciprofloxacin and more active than ofloxacin against *Enterobacteriaceae* and *P. aeruginosa*. Despite differences in in vitro activities, organisms relatively susceptible to one quinolone were relatively susceptible to all quinolones and organisms relatively resistant to one were relatively resistant to all. However, slopes for the lines of best fit comparing Bay y 3118 MICs with ciprofloxacin MICs were <1 for most species, indicating that the greater in vitro activity of Bay y 3118 was most pronounced against relatively resistant organisms.

When the in vitro activity of ciprofloxacin was compared with that of norfloxacin in 1983 (5), regression analysis of MICs (\log_2) indicated that the line of best fit had a slope close to unity, with r^2 being 0.92; ciprofloxacin was approximately fourfold more active than norfloxacin, and there was complete cross-susceptibility and cross-resistance independent of pharmacokinetic considerations. Subsequent studies with norfloxacin, ciprofloxacin, enoxacin, pefloxacin, ofloxacin, temafloxacin, lomefloxacin, fleroxacin, sparfloxacin, tosufloxacin, and several unnamed investigational quinolones have also reported high MIC correlations, particularly for Enterobacteriaceae (1, 3, 6, 7, 10). Although the mechanisms of resistance to the quinolones are not completely understood and the various guinolones may not be affected equally by all resistance mechanisms, the basic mechanisms of resistance are similar for all derivatives studied to date (4, 11). Pending pharmacokinetic and safety data for Bay y 3118, there is reasonable anticipation that its enhanced activity against gram-positive cocci and anaerobes would broaden the clinical utility of the quinolone class of antimicrobial agents.

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