

Comparison of the antibacterial activities of the quinolones Bay 12-8039, gatifloxacin (AM 1155), trovafloxacin, clinafloxacin, levofloxacin and ciprofloxacin

A. Bauernfeind*

Max von Pettenkofer-Institut, Pettenkoferstrasse 9a, 80336 Munich, Germany

The in-vitro activities of the quinolones Bay 12-8039, gatifloxacin (AM 1155), trovafloxacin, clinafloxacin, levofloxacin and ciprofloxacin were compared. Gram-positive cocci were most susceptible to Bay 12-8039, clinafloxacin and trovafloxacin; Enterobacteriaceae and fastidious organisms were most susceptible to ciprofloxacin; *Pseudomonas* spp. were most susceptible to clinafloxacin and ciprofloxacin; anaerobes, *Helicobacter pylori* and *Campylobacter jejuni* were most susceptible to gatifloxacin, clinafloxacin and trovafloxacin. Against Gram-positive cocci, the only agents that were more active than ciprofloxacin were those carrying an azabicyclo (trovafloxacin, Bay 12-8039), 3-amino-pyrrolidinyl (clinafloxacin) or 3-methyl-piperazinyl (gatifloxacin) moiety at position C₇.

Introduction

Quinolones established in the therapy of both nosocomial and community-acquired infections are relatively limited in their antibacterial activity against anaerobes, enterococci, staphylococci, glucose-non-fermenting Gram-negative rods¹ and recently also against Enterobacteriaceae (mainly *Escherichia coli* and *Klebsiella pneumoniae*).^{2–5} Modifications of the quinolone structure focus mainly on enhancing activity against these organisms. In addition, compounds with pharmacokinetics allowing once-daily dosing are favoured.

Recently a number of new quinolones, including Bay 12-8039,^{6,7} gatifloxacin (AM 1155),⁸ trovafloxacin (CP-99,129),⁹ clinafloxacin (CI-960, PD 127,391)¹⁰ and levofloxacin,¹¹ have reached or come close to clinical investigation. The antibacterial activities of these five quinolones were determined together with that of the established leader compound, ciprofloxacin, against a broad spectrum of bacterial pathogens (87 species). The results allow assessment of the activity of the new compounds against different groups of pathogens.

Materials and methods

Strains

Two thousand two hundred and ninety-four isolates of 87 species were cultured from specimens of blood, sputum

and urine, and from swabs of wound sites, ears, noses and throats. Only one isolate per patient was included.

Antibiotics

Bay 12-8039 and ciprofloxacin were obtained from Bayer AG (Wuppertal, Germany), gatifloxacin from Grünenthal GmbH (Stolberg, Germany), trovafloxacin from Pfizer GmbH (Karlsruhe, Germany), clinafloxacin from Parke-Davis, Warner-Lambert (Freiburg, Germany) and levofloxacin from Roussel Uclaf (Paris, France).

Determination of MICs

MICs were determined by an agar dilution technique. Mueller-Hinton agar (Difco, Augsburg, Germany) was the standard medium. An inoculum of 10⁴ cfu/spot (10⁵ cfu/spot for anaerobes) was delivered by a multipoint inoculator (Denley, Billingham, UK) to a series of agar plates that contained antibiotics in two-fold dilutions. Incubation was usually for 16 h (48 h for anaerobes, *Bordetella pertussis* and *Helicobacter pylori*) at 35°C. The MIC was determined as the lowest concentration of antibiotic at which no visible growth or growth of less than four colonies was observed. Mueller-Hinton agar was supplemented with 5% sheep blood for MIC determination of haemolytic streptococci, *Streptococcus milleri*, *Streptococcus mitior*, *Streptococcus pneumoniae* and *Listeria* spp. Chocolate agar

*Tel: +49-89-5160-5268; Fax: +49-89-5160-5266; E-mail: Adolf.Bauernfeind@mvp-bak.med.uni-muenchen.de

plates (peptone agar, Difco, plus 9% human erythrocytes and 2% horse serum) were incubated in a candle jar for growth of *Haemophilus* spp., *Neisseria gonorrhoeae* and *B. pertussis*. *H. pylori* was grown on Columbia agar (Unipath, Wesel, Germany) supplemented with 5% human blood in a microaerophilic atmosphere produced by a BR56 gas-generating kit (Unipath). Wilkins–Chalgren agar (Unipath) supplemented with 10% sheep blood frozen and thawed twice prior to addition, was used for anaerobes together with a BR38 gas-generating kit (Unipath).

E. coli ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Staphylococcus aureus* ATCC 29213 were used as reference strains.

Results

The MICs of ciprofloxacin for the reference strains *E. coli* ATCC 25922 (0.004–0.008 mg/L), *P. aeruginosa* ATCC 27853 (0.5–1 mg/L) and *S. aureus* ATCC 29213 (0.5 mg/L) were within the acceptable quality control ranges of the National Committee for Clinical Laboratory Standards.¹²

The majority of Enterobacteriaceae had MIC₉₀s of ≤1 mg/L of all six quinolones (Table). Clinafloxacin was the most active compound against all species including strains with ciprofloxacin MICs of >1 mg/L; it was two to four times more active than ciprofloxacin, Bay 12-8039 or gatifloxacin and four to eight times more active than levofloxacin or trovafloxacin. Activity against glucose-non-fermenting Gram-negative rods varied between species. The most active compounds against individual species were: ciprofloxacin and clinafloxacin against *Pseudomonas fluorescens* and *Pseudomonas putida* (MIC₉₀ = 0.5–2 mg/L), clinafloxacin against *P. aeruginosa* and *Alcaligenes xylosoxidans* (MIC₉₀ = 4 mg/L), trovafloxacin, Bay 12-8039 and gatifloxacin against *Stenotrophomonas maltophilia* (MIC₉₀ = 4 mg/L), clinafloxacin against *Burkholderia cepacia* (MIC₉₀ = 128 mg/L, MIC₅₀ = 1 mg/L).

Against staphylococci, the most active compounds were Bay 12-8039, trovafloxacin and clinafloxacin (MIC₉₀s = 0.06–0.25 mg/L), followed by gatifloxacin (MIC₉₀s = 0.13–0.5 mg/L), levofloxacin (MIC₉₀s = 0.25–1 mg/L) and ciprofloxacin (MIC₉₀s = 0.5–1 mg/L).

Against enterococci Bay 12-8039 and clinafloxacin were the most active quinolones (MIC₉₀s = 1–4 mg/L), and ciprofloxacin and levofloxacin were the least active (MIC₉₀s = 4–16 mg/L).

For *S. pneumoniae*, Bay 12-8039 and trovafloxacin had the lowest MIC₉₀s (0.25 mg/L), and ciprofloxacin and levofloxacin the highest MIC₉₀s (2 mg/L). Susceptibility of non-pneumococcal streptococci was high for Bay 12-8039, trovafloxacin, clinafloxacin and gatifloxacin (MIC₉₀s = 0.13–0.5 mg/L) and lower for ciprofloxacin and levofloxacin (MIC₉₀s = 1–2 mg/L).

All the fastidious organisms included were highly susceptible to all six quinolones (MIC₉₀s = 0.004–0.06 mg/L), with clinafloxacin being the most active.

Against both *H. pylori* and *Campylobacter jejuni*, Bay 12-8039, trovafloxacin, clinafloxacin and gatifloxacin showed equal activity (MIC₉₀s = 0.13–0.25 mg/L); ciprofloxacin and levofloxacin were less active (MIC₉₀s = 0.5–1 mg/L).

Against *Bacteroides* spp., trovafloxacin, clinafloxacin and gatifloxacin were the most active compounds (MIC₉₀s = 1–2 mg/L), followed by Bay 12-8039 and levofloxacin (MIC₉₀s = 2–4 mg/L) and ciprofloxacin (MIC₉₀s = 8–16 mg/L). *Clostridium* spp. were generally more susceptible than *Clostridium difficile*. By MIC₉₀, trovafloxacin, clinafloxacin, Bay 12-8039 and gatifloxacin were about equally active against *C. difficile* (MIC₉₀ = 1–2 mg/L), followed by levofloxacin (MIC₉₀ = 8 mg/L) and ciprofloxacin (MIC₉₀ = 32 mg/L).

Discussion

The quinolone compounds studied differ in their structures mainly at positions R₁, R₇ and X₈ (Figure).¹³ The data allow discussion of specific structure–activity relationships similar to the analysis of Domagala.¹³ The enhanced activity of some of the new quinolones observed against Gram-positive cocci in comparison with ciprofloxacin (four to eight times) was found to be restricted to structures that carry at position C₇ an azabicyclo (trovafloxacin, Bay 12-8039, MIC₉₀s 0.06–0.25 mg/L), 3-amino-pyrrolidinyl (clinafloxacin, MIC₉₀s 0.06–0.25 mg/L) or 3-methyl-piperazinyl (gatifloxacin, MIC₉₀s 0.13–0.5 mg/L) moiety, but not a 4-methyl-piperazinyl moiety (levofloxacin, MIC₉₀s 0.25–1 mg/L). Activity against Enterobacteriaceae at a level similar to ciprofloxacin was observed only for compounds with a cyclopropyl group at position N₁ (Bay 12-8039, gatifloxacin, clinafloxacin). In contrast, trovafloxacin (2,4-difluorophenyl group) and levofloxacin (benzoxazine bridge between C₈ and N₁) were two to four times less active against these organisms. The methoxy group at position C₈ in both Bay 12-8039 and gatifloxacin appears not to have a noticeable effect on antibacterial potency and spectrum even against anaerobes, since quinolones without this substitution (e.g. trovafloxacin) show equal activity.

Major causative organisms of infections of the upper and

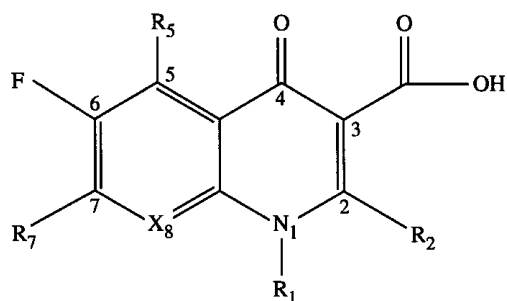


Figure. Major positions of substituents in structural variants of quinolones.¹³

In-vitro activities of new quinolones

Table. Comparative in-vitro activities of 4-quinolones

Species (n)	Compound	range	MIC (mg/L)		
			MIC ₅₀	MIC ₉₀	
<i>E. coli</i>	ampicillin ≤ 8 mg/L (30)	Bay 12-8039	0.002–0.06	0.008	0.008
		gatifloxacin	0.008–0.06	0.008	0.016
		ciprofloxacin	0.004–0.06	0.008	0.016
		trovafloxacin	0.008–0.13	0.016	0.03
		clinafloxacin	0.002–0.06	0.004	0.008
		levofloxacin	0.008–0.13	0.016	0.03
	ampicillin ≥ 16 mg/L (78)	Bay 12-8039	0.002–256	0.016	8
		gatifloxacin	0.004–128	0.03	8
		ciprofloxacin	0.004–128	0.016	16
		trovafloxacin	0.008–256	0.03	32
		clinafloxacin	0.002–128	0.008	4
		levofloxacin	0.008–256	0.03	16
	ceftazidime ≥ 16 mg/L (13)	Bay 12-8039	0.002–4	0.008	4
		gatifloxacin	0.008–8	0.03	4
		ciprofloxacin	0.004–8	0.016	4
		trovafloxacin	0.008–8	0.03	8
		clinafloxacin	0.002–4	0.008	2
		levofloxacin	0.008–16	0.03	8
<i>K. pneumoniae</i>	ceftazidime ≤ 8 mg/L (61)	Bay 12-8039	0.016–64	0.03	0.13
		gatifloxacin	0.008–32	0.03	0.13
		ciprofloxacin	0.004–64	0.016	0.06
		trovafloxacin	0.016–64	0.03	0.13
		clinafloxacin	0.004–32	0.008	0.03
		levofloxacin	0.008–64	0.03	0.13
	ceftazidime ≥ 16 mg/L (25)	Bay 12-8039	0.008–16	0.13	8
		gatifloxacin	0.008–32	0.06	4
		ciprofloxacin	0.004–16	0.06	8
		trovafloxacin	0.016–32	0.13	16
		clinafloxacin	0.002–4	0.03	2
		levofloxacin	0.008–32	0.13	16
<i>Klebsiella oxytoca</i>	ceftazidime ≤ 8 mg/L (64)	Bay 12-8039	0.002–1	0.003	0.13
		gatifloxacin	0.004–0.5	0.016	0.06
		ciprofloxacin	0.002–0.5	0.016	0.06
		trovafloxacin	0.004–1	0.03	0.13
		clinafloxacin	0.004–0.25	0.016	0.03
		levofloxacin	0.008–1	0.03	0.13
	ceftazidime ≥ 16 mg/L (5)	Bay 12-8039	0.008–0.25	0.06	0.25
		gatifloxacin	0.008–0.13	0.03	0.13
		ciprofloxacin	0.004–0.13	0.03	0.13
		trovafloxacin	0.004–0.25	0.06	0.25
		clinafloxacin	0.004–0.06	0.016	0.06
		levofloxacin	0.008–0.25	0.06	0.25
<i>Enterobacter cloacae</i> (63)	Bay 12-8039	0.016–16	0.03	0.06	
	gatifloxacin	0.008–32	0.016	0.06	
	ciprofloxacin	0.008–16	0.016	0.03	
	trovafloxacin	0.008–16	0.03	0.06	
	clinafloxacin	0.004–2	0.008	0.016	
	levofloxacin	0.016–32	0.03	0.06	
<i>Enterobacter aerogenes</i> (42)	Bay 12-8039	0.03–4	0.06	2	
	gatifloxacin	0.008–2	0.06	1	
	ciprofloxacin	0.008–2	0.03	1	

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Table. *Continued*

Species (<i>n</i>)	Compound	range	MIC (mg/L)	
			MIC ₅₀	MIC ₉₀
<i>Enterobacter agglomerans</i> (16)	trovafloxacin	0.016–4	0.06	2
	clinafloxacin	0.004–1	0.016	0.5
	levofloxacin	0.016–4	0.06	4
	Bay 12-8039	0.004–2	0.03	2
	gatifloxacin	0.004–1	0.016	1
	ciprofloxacin	0.002–2	0.016	1
	trovafloxacin	0.002–2	0.03	2
	clinafloxacin	0.002–1	0.008	0.5
<i>Enterobacter intermedius</i> (6)	levofloxacin	0.004–4	0.03	2
	Bay 12-8039	0.03–0.06	0.03	0.06
	gatifloxacin	0.008–0.06	0.016	0.06
	ciprofloxacin	0.016–0.03	0.016	0.03
	trovafloxacin	0.03–0.06	0.03	0.06
	clinafloxacin	0.008–0.016	0.008	0.016
<i>Enterobacter sakazakii</i> (18)	levofloxacin	0.016–0.06	0.03	0.06
	Bay 12-8039	0.004–0.13	0.016	0.03
	gatifloxacin	0.004–0.03	0.016	0.03
	ciprofloxacin	0.002–0.016	0.008	0.016
	trovafloxacin	0.004–0.03	0.016	0.03
	clinafloxacin	0.002–0.008	0.004	0.008
<i>Citrobacter freundii</i> (52)	levofloxacin	0.004–0.03	0.016	0.03
	Bay 12-8039	0.016–64	0.06	1
	gatifloxacin	0.008–32	0.06	1
	ciprofloxacin	0.004–64	0.016	0.25
	trovafloxacin	0.008–64	0.06	1
	clinafloxacin	0.004–16	0.008	0.06
<i>Citrobacter diversus</i> (20)	levofloxacin	0.016–128	0.03	0.5
	Bay 12-8039	0.016–1	0.06	0.25
	gatifloxacin	0.016–2	0.06	0.25
	ciprofloxacin	0.004–0.5	0.016	0.06
	trovafloxacin	0.016–1	0.06	0.25
	clinafloxacin	0.002–0.13	0.016	0.13
<i>Hafnia alvei</i> (31)	levofloxacin	0.008–1	0.03	0.13
	Bay 12-8039	0.008–0.25	0.06	0.13
	gatifloxacin	0.008–0.06	0.016	0.06
	ciprofloxacin	0.004–0.06	0.016	0.03
	trovafloxacin	0.004–0.06	0.016	0.03
	clinafloxacin	0.004–0.016	0.008	0.016
<i>Serratia marcescens</i> (55)	levofloxacin	0.008–0.13	0.03	0.13
	Bay 12-8039	0.06–128	0.25	8
	gatifloxacin	0.016–64	0.25	4
	ciprofloxacin	0.008–64	0.13	4
	trovafloxacin	0.03–128	0.5	8
	clinafloxacin	0.004–32	0.06	2
<i>Serratia liquefaciens</i> (32)	levofloxacin	0.016–64	0.25	8
	Bay 12-8039	0.03–32	0.13	1
	gatifloxacin	0.016–64	0.06	1
	ciprofloxacin	0.008–16	0.03	0.5
	trovafloxacin	0.03–32	0.13	1
	clinafloxacin	0.004–8	0.016	0.25
	levofloxacin	0.016–32	0.06	1

In-vitro activities of new quinolones

Table. Continued

Species (n)	Compound	range	MIC (mg/L)	
			MIC ₅₀	MIC ₉₀
<i>Proteus mirabilis</i> (37)	Bay 12-8039	0.016–16	0.06	0.25
	gatifloxacin	0.06–64	0.13	0.25
	ciprofloxacin	0.016–16	0.016	0.06
	trovafloxacin	0.06–8	0.25	0.5
	clinafloxacin	0.008–8	0.016	0.06
	levofloxacin	0.03–32	0.03	0.25
<i>Proteus vulgaris</i> (35)	Bay 12-8039	0.06–0.5	0.25	0.5
	gatifloxacin	0.03–0.25	0.13	0.25
	ciprofloxacin	0.008–0.06	0.03	0.06
	trovafloxacin	0.06–0.5	0.25	0.5
	clinafloxacin	0.004–0.03	0.016	0.03
	levofloxacin	0.016–0.13	0.06	0.13
<i>Providencia rettgeri</i> (33)	Bay 12-8039	0.06–8	0.13	0.5
	gatifloxacin	0.06–4	0.13	0.5
	ciprofloxacin	0.016–8	0.03	0.25
	trovafloxacin	0.03–16	0.06	0.25
	clinafloxacin	0.016–4	0.016	0.06
	levofloxacin	0.03–16	0.06	0.5
<i>Providencia stuartii</i> (30)	Bay 12-8039	0.03–4	0.06	0.5
	gatifloxacin	0.03–8	0.06	0.5
	ciprofloxacin	0.008–8	0.016	0.13
	trovafloxacin	0.016–4	0.03	0.25
	clinafloxacin	0.004–4	0.008	0.06
	levofloxacin	0.03–16	0.03	0.25
<i>Providencia alcalifaciens</i> (6)	Bay 12-8039	0.016–0.5	0.03	0.5
	gatifloxacin	0.03–0.5	0.03	0.5
	ciprofloxacin	0.008–0.25	0.008	0.25
	trovafloxacin	0.016–1	0.03	1
	clinafloxacin	0.004–0.06	0.016	0.06
	levofloxacin	0.016–0.5	0.06	0.5
<i>Morganella morganii</i> (41)	Bay 12-8039	0.03–8	0.06	0.13
	gatifloxacin	0.03–4	0.06	0.25
	ciprofloxacin	0.008–2	0.016	0.03
	trovafloxacin	0.008–4	0.016	0.03
	clinafloxacin	0.008–2	0.008	0.03
	levofloxacin	0.016–4	0.03	0.06
<i>Shigella</i> spp. ^b (22)	Bay 12-8039	0.016–0.03	0.016	0.03
	gatifloxacin	0.004–0.016	0.016	0.016
	ciprofloxacin	0.004–0.008	0.008	0.008
	trovafloxacin	0.008–0.016	0.016	0.016
	clinafloxacin	0.002–0.004	0.004	0.004
	levofloxacin	0.008–0.016	0.016	0.016
<i>Salmonella</i> spp. ^b (20)	Bay 12-8039	0.016–0.25	0.06	0.13
	gatifloxacin	0.008–0.13	0.03	0.06
	ciprofloxacin	0.004–0.06	0.016	0.016
	trovafloxacin	0.008–0.06	0.016	0.03
	clinafloxacin	0.002–0.03	0.008	0.008
	levofloxacin	0.008–0.13	0.03	0.03
<i>Yersinia enterocolitica</i> (16)	Bay 12-8039	0.016–0.06	0.03	0.06
	gatifloxacin	0.03–0.06	0.03	0.06
	ciprofloxacin	0.008–0.016	0.008	0.016

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Table. Continued

Species (<i>n</i>)	Compound	range	MIC (mg/L)	
			MIC ₅₀	MIC ₉₀
<i>Acinetobacter baumannii</i> (43)	trovafloxacin	0.016–0.03	0.016	0.03
	clinafloxacin	0.004–0.008	0.004	0.008
	levofloxacin	0.016–0.03	0.016	0.03
	Bay 12-8039	0.008–2	0.03	0.25
	gatifloxacin	0.008–2	0.06	0.25
	ciprofloxacin	0.03–4	0.13	1
	trovafloxacin	0.004–2	0.03	0.13
<i>Acinetobacter lwoffii</i> (30)	clinafloxacin	0.016–1	0.03	0.13
	levofloxacin	0.03–2	0.06	0.5
	Bay 12-8039	0.008–0.03	0.016	0.03
	gatifloxacin	0.016–0.06	0.016	0.06
	ciprofloxacin	0.03–0.13	0.06	0.13
	trovafloxacin	0.008–0.03	0.008	0.03
	clinafloxacin	0.004–0.06	0.016	0.03
<i>Acinetobacter johnsonii</i> (15)	levofloxacin	0.03–0.13	0.03	0.13
	Bay 12-8039	0.004–0.03	0.016	0.03
	gatifloxacin	0.002–0.06	0.016	0.06
	ciprofloxacin	0.008–0.13	0.06	0.13
	trovafloxacin	0.002–0.06	0.016	0.03
	clinafloxacin	0.004–0.03	0.016	0.03
	levofloxacin	0.008–0.13	0.06	0.06
<i>Acinetobacter calcoaceticus</i> (20)	Bay 12-8039	0.008–0.06	0.016	0.06
	gatifloxacin	0.016–0.06	0.016	0.03
	ciprofloxacin	0.03–0.25	0.13	0.13
	trovafloxacin	0.008–0.03	0.008	0.03
	clinafloxacin	0.008–0.06	0.016	0.03
	levofloxacin	0.03–0.25	0.06	0.13
	Bay 12-8039	0.008–0.06	0.016	0.06
<i>Acinetobacter</i> genospecies 3 (12)	gatifloxacin	0.016–0.06	0.016	0.03
	ciprofloxacin	0.03–0.25	0.13	0.13
	trovafloxacin	0.008–0.03	0.008	0.03
	clinafloxacin	0.008–0.06	0.016	0.03
	levofloxacin	0.03–0.25	0.06	0.13
	Bay 12-8039	0.008–0.06	0.016	0.06
	gatifloxacin	0.016–0.06	0.016	0.03
<i>Acinetobacter</i> genospecies 12 (6)	ciprofloxacin	0.03–0.25	0.13	0.13
	trovafloxacin	0.008–0.03	0.008	0.03
	clinafloxacin	0.008–0.06	0.016	0.03
	levofloxacin	0.03–0.25	0.06	0.13
	Bay 12-8039	0.002–0.016	0.016	0.016
	gatifloxacin	0.002–0.03	0.016	0.03
	ciprofloxacin	0.008–0.06	0.06	0.06
<i>Acinetobacter</i> strain 84 (14)	trovafloxacin	0.002–0.03	0.016	0.03
	clinafloxacin	0.004–0.016	0.016	0.03
	levofloxacin	0.016–0.06	0.03	0.06
	Bay 12-8039	0.016–1	0.016	0.5
	gatifloxacin	0.016–1	0.016	0.5
	ciprofloxacin	0.06–2	0.06	2
	trovafloxacin	0.008–1	0.016	0.5
<i>Aeromonas hydrophila</i> (32)	clinafloxacin	0.03–1	0.03	0.5
	levofloxacin	0.016–1	0.03	0.5
	Bay 12-8039	0.008–0.06	0.016	0.03
	gatifloxacin	0.008–0.06	0.016	0.03
	ciprofloxacin	0.002–0.016	0.004	0.008
	trovafloxacin	0.002–0.03	0.004	0.008
	clinafloxacin	0.002–0.016	0.004	0.008
levofloxacin	0.004–0.06	0.016	0.03	

In-vitro activities of new quinolones

Table. Continued

Species (n)	Compound	range	MIC (mg/L)	
			MIC ₅₀	MIC ₉₀
<i>A. xylosoxidans</i> (17)	Bay 12-8039	2–16	4	8
	gatifloxacin	4–16	8	16
	ciprofloxacin	2–8	4	8
	trovafloxacin	2–32	8	32
	clinafloxacin	0.5–4	2	4
	levofloxacin	4–16	8	16
<i>P. aeruginosa</i> (50)	Bay 12-8039	0.5–128	4	32
	gatifloxacin	0.5–128	4	32
	ciprofloxacin	0.06–32	0.5	8
	trovafloxacin	0.25–64	2	16
	clinafloxacin	0.03–16	0.25	4
	levofloxacin	0.25–64	2	32
<i>P. fluorescens</i> (31)	Bay 12-8039	0.13–16	0.5	4
	gatifloxacin	0.13–16	0.5	4
	ciprofloxacin	0.03–4	0.13	2
	trovafloxacin	0.06–8	0.5	8
	clinafloxacin	0.03–1	0.13	0.5
	levofloxacin	0.13–8	0.5	4
<i>Pseudomonas stutzeri</i> (10)	Bay 12-8039	0.06–0.5	0.25	0.5
	gatifloxacin	0.06–0.25	0.13	0.25
	ciprofloxacin	0.016–0.06	0.03	0.06
	trovafloxacin	0.06–0.13	0.13	0.13
	clinafloxacin	0.016–0.06	0.03	0.06
	levofloxacin	0.06–0.5	0.13	0.5
<i>P. putida</i> (20)	Bay 12-8039	0.25–16	0.5	4
	gatifloxacin	0.25–16	0.5	4
	ciprofloxacin	0.06–4	0.13	1
	trovafloxacin	0.25–8	0.5	8
	clinafloxacin	0.06–2	0.13	1
	levofloxacin	0.13–8	0.25	2
<i>B. cepacia</i> (54)	Bay 12-8039	0.03–512	4	256
	gatifloxacin	0.03–256	2	256
	ciprofloxacin	0.03–256	2	256
	trovafloxacin	0.03–256	2	256
	clinafloxacin	0.016–128	1	128
	levofloxacin	0.13–512	2	128
<i>Ralstonia pickettii</i> (10)	Bay 12-8039	0.016–0.25	0.13	0.25
	gatifloxacin	0.016–0.25	0.13	0.25
	ciprofloxacin	0.06–0.5	0.13	0.25
	trovafloxacin	0.016–0.25	0.06	0.13
	clinafloxacin	0.06–0.25	0.13	0.25
	levofloxacin	0.06–1	0.5	0.5
<i>S. maltophilia</i> (50)	Bay 12-8039	0.06–32	0.13	4
	gatifloxacin	0.06–32	0.25	4
	ciprofloxacin	0.25–128	0.5	16
	trovafloxacin	0.06–64	0.25	4
	clinafloxacin	0.13–32	0.25	8
	levofloxacin	0.13–64	0.25	8
<i>Haemophilus influenzae</i> AMP ≤ 8 mg/L (46)	Bay 12-8039	0.008–0.13	0.016	0.06
	gatifloxacin	0.004–0.016	0.008	0.016
	ciprofloxacin	0.004–0.016	0.008	0.016

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Table. Continued

Species (<i>n</i>)	Compound	range	MIC (mg/L)	
			MIC ₅₀	MIC ₉₀
ampicillin \geq 16 mg/L (28)	trovafloxacin	0.004–0.03	0.008	0.016
	clinafloxacin	0.002–0.008	0.004	0.004
	levofloxacin	0.008–0.06	0.03	0.06
	Bay 12-8039	0.008–0.13	0.016	0.06
	gatifloxacin	0.004–0.016	0.008	0.016
	ciprofloxacin	0.004–0.016	0.008	0.016
	trovafloxacin	0.004–0.03	0.008	0.016
	clinafloxacin	0.002–0.008	0.004	0.004
<i>Haemophilus parainfluenzae</i> (11)	levofloxacin	0.008–0.06	0.03	0.06
	Bay 12-8039	0.004–0.06	0.008	0.03
	gatifloxacin	0.002–0.016	0.004	0.016
	ciprofloxacin	0.002–0.016	0.004	0.016
	trovafloxacin	0.002–0.03	0.004	0.016
	clinafloxacin	0.002–0.008	0.004	0.004
	levofloxacin	0.004–0.03	0.016	0.06
	Bay 12-8039	0.004–0.03	0.016	0.03
<i>M. catarrhalis</i> β -lactamase-negative (8)	gatifloxacin	0.004–0.03	0.03	0.03
	ciprofloxacin	0.004–0.03	0.016	0.03
	trovafloxacin	0.002–0.03	0.016	0.03
	clinafloxacin	0.004–0.008	0.008	0.008
	levofloxacin	0.016–0.03	0.016	0.03
	Bay 12-8039	0.016–0.03	0.03	0.03
	gatifloxacin	0.008–0.03	0.03	0.03
	ciprofloxacin	0.008–0.03	0.016	0.03
β -lactamase-positive (52)	trovafloxacin	0.008–0.03	0.016	0.016
	clinafloxacin	0.004–0.008	0.004	0.008
	levofloxacin	0.016–0.03	0.016	0.03
	Bay 12-8039	0.004–0.06	0.008	0.016
	gatifloxacin	0.002–0.016	0.004	0.016
	ciprofloxacin	0.002–0.016	0.004	0.008
	trovafloxacin	0.002–0.03	0.004	0.008
	clinafloxacin	0.002–0.008	0.004	0.008
<i>N. gonorrhoeae</i> ampicillin \leq 8 mg/L (20)	levofloxacin	0.004–0.03	0.008	0.016
	Bay 12-8039	0.016–0.06	0.016	0.03
	gatifloxacin	0.002–0.016	0.004	0.016
	ciprofloxacin	0.002–0.016	0.004	0.008
	trovafloxacin	0.002–0.03	0.004	0.008
	clinafloxacin	0.002–0.008	0.004	0.008
	levofloxacin	0.004–0.03	0.008	0.016
	Bay 12-8039	0.016–0.06	0.016	0.03
ampicillin \geq 16 mg/L (14)	gatifloxacin	0.008–0.03	0.016	0.016
	ciprofloxacin	0.008–0.03	0.008	0.016
	trovafloxacin	0.004–0.016	0.008	0.008
	clinafloxacin	0.008–0.016	0.008	0.008
	levofloxacin	0.008–0.03	0.016	0.016
	Bay 12-8039	0.002–0.016	0.004	0.016
	gatifloxacin	0.001–0.008	0.004	0.008
	ciprofloxacin	0.001–0.008	0.004	0.008
<i>B. pertussis</i> (11)	trovafloxacin	0.002–0.008	0.004	0.008
	clinafloxacin	0.008–0.03	0.016	0.03
	levofloxacin	0.008–0.03	0.016	0.03
	Bay 12-8039	0.016–0.13	0.03	0.06
	gatifloxacin	0.03–0.25	0.06	0.13
	ciprofloxacin	0.13–0.5	0.25	0.5
	trovafloxacin	0.008–0.13	0.03	0.06
	clinafloxacin	0.008–0.06	0.03	0.06
<i>S. aureus</i> methicillin-sensitive (90)	levofloxacin	0.06–0.25	0.13	0.25

In-vitro activities of new quinolones

Table. Continued

Species (n)	Compound	range	MIC (mg/L)	
			MIC ₅₀	MIC ₉₀
methicillin-resistant (63)	Bay 12-8039	0.016–8	0.06	4
	gatifloxacin	0.03–16	0.13	16
	ciprofloxacin	0.25–128	1	32
	trovafloxacin	0.016–8	0.13	4
	clinafloxacin	0.03–16	0.06	8
	levofloxacin	0.25–32	0.5	16
<i>Staphylococcus epidermidis</i> methicillin-sensitive (39)	Bay 12-8039	0.03–2	0.06	0.13
	gatifloxacin	0.06–4	0.13	0.25
	ciprofloxacin	0.13–8	0.5	1
	trovafloxacin	0.03–2	0.06	0.13
	clinafloxacin	0.03–1	0.06	0.25
	levofloxacin	0.13–4	0.5	0.5
methicillin-resistant (26)	Bay 12-8039	0.03–0.5	0.06	0.13
	gatifloxacin	0.06–1	0.13	0.25
	ciprofloxacin	0.13–4	0.5	1
	trovafloxacin	0.016–1	0.03	0.25
	clinafloxacin	0.03–0.5	0.06	0.25
	levofloxacin	0.13–2	0.5	1
<i>Staphylococcus haemolyticus</i> methicillin-sensitive (34)	Bay 12-8039	0.006–2	0.06	0.13
	gatifloxacin	0.06–4	0.13	0.5
	ciprofloxacin	0.25–32	0.5	1
	trovafloxacin	0.03–4	0.06	0.13
	clinafloxacin	0.03–1	0.06	0.13
	levofloxacin	0.13–16	0.5	1
methicillin-resistant (20)	Bay 12-8039	0.03–2	0.06	0.13
	gatifloxacin	0.06–8	0.13	0.25
	ciprofloxacin	0.13–32	0.5	1
	trovafloxacin	0.016–4	0.03	0.25
	clinafloxacin	0.016–1	0.06	0.13
	levofloxacin	0.13–16	0.25	1
<i>Staphylococcus saprophyticus</i> methicillin-sensitive (20)	Bay 12-8039	0.03–0.13	0.03	0.06
	gatifloxacin	0.06–0.25	0.06	0.13
	ciprofloxacin	0.25–1	0.25	0.5
	trovafloxacin	0.016–0.13	0.06	0.06
	clinafloxacin	0.03–0.13	0.03	0.06
	levofloxacin	0.25–1	0.25	0.5
methicillin-resistant (20)	Bay 12-8039	0.03–4	0.06	1
	gatifloxacin	0.06–16	0.13	8
	ciprofloxacin	0.25–64	0.5	16
	trovafloxacin	0.03–4	0.06	1
	clinafloxacin	0.03–2	0.06	0.5
	levofloxacin	0.25–32	0.5	8
<i>Staphylococcus hominis</i> (29)	Bay 12-8039	0.03–0.5	0.03	0.06
	gatifloxacin	0.06–2	0.13	0.25
	ciprofloxacin	0.13–8	0.5	1
	trovafloxacin	0.03–1	0.06	0.13
	clinafloxacin	0.03–0.25	0.06	0.06
	levofloxacin	0.25–4	0.5	1
<i>Staphylococcus cohnii</i> (21)	Bay 12-8039	0.03–0.5	0.03	0.06
	gatifloxacin	0.06–1	0.06	0.13
	ciprofloxacin	0.25–4	0.25	0.5

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Table. *Continued*

Species (<i>n</i>)	Compound	range	MIC (mg/L)		
			MIC ₅₀	MIC ₉₀	
<i>Staphylococcus simulans</i> (20)	trovafloxacin	0.016–1	0.06	0.06	
	clinafloxacin	0.03–0.25	0.03	0.06	
	levofloxacin	0.25–2	0.25	0.5	
	Bay 12-8039	0.016–0.06	0.03	0.06	
	gatifloxacin	0.03–0.13	0.06	0.13	
	ciprofloxacin	0.13–0.5	0.25	0.5	
	trovafloxacin	0.008–0.06	0.06	0.06	
<i>Staphylococcus warneri</i> (7)	clinafloxacin	0.016–0.06	0.03	0.06	
	levofloxacin	0.13–0.5	0.25	0.5	
	Bay 12-8039	0.03–0.06	0.03	0.06	
	gatifloxacin	0.06–0.13	0.13	0.13	
	ciprofloxacin	0.13–0.5	0.25	0.5	
	trovafloxacin	0.03–0.06	0.06	0.06	
	clinafloxacin	0.016–0.06	0.06	0.06	
<i>Staphylococcus xylosus</i> (6)	levofloxacin	0.13–0.25	0.25	0.25	
	Bay 12-8039	0.03–0.06	0.06	0.06	
	gatifloxacin	0.13	0.13	0.13	
	ciprofloxacin	0.25–0.5	0.25	0.5	
	trovafloxacin	0.03–0.06	0.06	0.06	
	clinafloxacin	0.06	0.06	0.06	
	levofloxacin	0.25–0.5	0.25	0.5	
<i>S. pneumoniae</i>	Bay 12-8039	0.03–0.25	0.13	0.25	
	penicillin ≤ 0.06 mg/L (30)	gatifloxacin	0.06–1	0.25	1
		ciprofloxacin	0.25–4	1	4
		trovafloxacin	0.03–0.25	0.13	0.25
		clinafloxacin	0.06–1	0.13	0.5
		levofloxacin	0.25–2	1	2
	penicillin = 0.13–0.5 mg/L (20)	Bay 12-8039	0.03–0.25	0.13	0.25
		gatifloxacin	0.13–1	0.25	0.5
		ciprofloxacin	0.5–4	1	2
		trovafloxacin	0.03–0.25	0.13	0.25
		clinafloxacin	0.06–1	0.13	0.5
		levofloxacin	0.25–2	1	2
	penicillin = 1–4 mg/L (15)	Bay 12-8039	0.03–0.25	0.13	0.25
		gatifloxacin	0.13–1	0.25	0.5
	ciprofloxacin	0.5–4	1	2	
	trovafloxacin	0.03–0.25	0.13	0.25	
	clinafloxacin	0.06–1	0.13	0.5	
	levofloxacin	0.25–2	1	2	
<i>Streptococcus pyogenes</i> (47)	Bay 12-8039	0.06–0.5	0.25	0.25	
	gatifloxacin	0.06–1	0.25	0.5	
	ciprofloxacin	0.25–2	1	1	
	trovafloxacin	0.06–1	0.25	0.25	
	clinafloxacin	0.06–0.5	0.5	0.5	
	levofloxacin	0.5–1	1	1	
	Bay 12-8039	0.06–0.5	0.25	0.5	
<i>Streptococcus agalactiae</i> (38)	gatifloxacin	0.06–1	0.25	0.5	
	ciprofloxacin	0.25–2	1	2	
	trovafloxacin	0.06–1	0.25	0.5	
	clinafloxacin	0.06–0.25	0.13	0.25	
	levofloxacin	0.5–1	0.5	1	

In-vitro activities of new quinolones

Table. Continued

Species (n)	Compound	range	MIC (mg/L)		
			MIC ₅₀	MIC ₉₀	
Haemolytic streptococci group C (8)	Bay 12-8039	0.06–0.13	0.13	0.13	
	gatifloxacin	0.13–0.25	0.13	0.25	
	ciprofloxacin	0.5–1	0.5	1	
	trovafloxacin	0.13–0.25	0.13	0.25	
	clinafloxacin	0.13–0.25	0.25	0.5	
	levofloxacin	0.5–1	0.5	1	
	group G (22)	Bay 12-8039	0.06–0.13	0.13	0.13
		gatifloxacin	0.13–0.25	0.13	0.25
		ciprofloxacin	0.25–1	0.5	1
		trovafloxacin	0.06–0.25	0.06	0.13
clinafloxacin		0.06–0.25	0.25	0.25	
<i>S. milleri</i> group (22)	levofloxacin	0.25–1	0.5	1	
	Bay 12-8039	0.03–0.13	0.06	0.06	
	gatifloxacin	0.06–1	0.25	0.5	
	ciprofloxacin	0.5–4	1	2	
	trovafloxacin	0.03–0.25	0.06	0.13	
	clinafloxacin	0.06–0.25	0.13	0.25	
<i>S. mitior</i> (5)	levofloxacin	0.5–4	0.5	2	
	Bay 12-8039	0.06–0.13	0.06	0.13	
	gatifloxacin	0.25–0.5	0.25	0.5	
	ciprofloxacin	1–2	1	2	
	trovafloxacin	0.06–0.13	0.13	0.13	
	clinafloxacin	0.06–0.25	0.13	0.25	
<i>Enterococcus faecalis</i> (100)	levofloxacin	0.5–2	2	2	
	Bay 12-8039	0.13–1	0.25	1	
	gatifloxacin	0.25–4	0.5	2	
	ciprofloxacin	0.5–8	1	4	
	trovafloxacin	0.13–4	0.5	2	
	clinafloxacin	0.25–4	0.5	1	
<i>Enterococcus faecium</i> (40)	levofloxacin	0.25–4	1	2	
	Bay 12-8039	0.13–8	1	4	
	gatifloxacin	0.13–8	2	4	
	ciprofloxacin	0.25–32	4	16	
	trovafloxacin	0.13–16	2	8	
	clinafloxacin	0.25–16	1	4	
<i>Enterococcus gallinarum</i> (5)	levofloxacin	0.5–32	2	8	
	Bay 12-8039	0.25–2	0.5	2	
	gatifloxacin	0.5–4	1	4	
	ciprofloxacin	1–8	2	8	
	trovafloxacin	0.25–2	0.5	2	
	clinafloxacin	0.25–2	0.5	2	
<i>Listeria</i> spp. ^c (14)	levofloxacin	1–8	2	8	
	Bay 12-8039	0.13–0.5	0.25	0.5	
	gatifloxacin	0.5	0.5	0.5	
	ciprofloxacin	1–2	1	1	
	trovafloxacin	0.06–1	0.25	0.5	
	clinafloxacin	0.25–0.5	0.25	0.5	
<i>H. pylori</i> (14)	levofloxacin	0.5–2	1	2	
	Bay 12-8039	0.06–0.13	0.06	0.13	
	gatifloxacin	0.13–0.25	0.13	0.25	
	ciprofloxacin	0.25–0.5	0.25	0.5	

Table. Continued

Species (n)	Compound	range	MIC (mg/L)	
			MIC ₅₀	MIC ₉₀
<i>C. jejuni</i> (18)	trovafloxacin	0.06–0.13	0.06	0.13
	clinafloxacin	0.06–0.13	0.06	0.13
	levofloxacin	0.13–0.5	0.25	0.5
	Bay 12-8039	0.03–0.13	0.03	0.13
	gatifloxacin	0.06–0.25	0.13	0.25
	ciprofloxacin	0.13–1	0.25	1
	trovafloxacin	0.03–0.13	0.06	0.13
	clinafloxacin	0.06–0.25	0.06	0.25
<i>C. difficile</i> (20)	levofloxacin	0.06–0.5	0.13	0.5
	Bay 12-8039	0.13–2	1	2
	gatifloxacin	0.25–2	1	2
	ciprofloxacin	2–32	8	32
	trovafloxacin	0.13–1	0.5	1
	clinafloxacin	0.13–1	0.5	1
	levofloxacin	1–8	2	8
	Bay 12-8039	0.06–0.25	0.06	0.13
<i>Clostridium</i> spp. ^d (5)	gatifloxacin	0.06–0.5	0.25	0.5
	ciprofloxacin	0.25–2	0.5	2
	trovafloxacin	0.03–0.5	0.13	0.5
	clinafloxacin	0.06–0.25	0.06	0.25
	levofloxacin	0.06–1	0.13	1
	Bay 12-8039	0.25–4	1	2
	gatifloxacin	0.25–8	0.5	1
	ciprofloxacin	2–32	8	8
<i>Bacteroides fragilis</i> (20)	trovafloxacin	0.13–8	0.5	1
	clinafloxacin	0.5–4	0.5	2
	levofloxacin	2–8	2	2
	Bay 12-8039	0.13–4	0.5	4
	gatifloxacin	0.13–2	0.5	2
	ciprofloxacin	1–16	8	16
	trovafloxacin	0.13–4	0.5	2
	clinafloxacin	0.5–2	0.5	2
<i>Bacteroides</i> spp. ^e (6)	levofloxacin	1–4	2	4

^aSeventeen *Shigella flexneri*, three *Shigella sonnei* and two *Shigella boydii*.

^bThirteen *Salmonella typhimurium*, three *Salmonella enteritidis*, and one each of *Salmonella agona*, *Salmonella brandenburg*, *Salmonella infantis* and *Salmonella minnesota*.

^cTen *Listeria monocytogenes* and one each of *Listeria innocua*, *Listeria ivanovii*, *Listeria seeligeri* and *Listeria welshmeri*.

^dOne each of *Clostridium histolyticum*, *Clostridium perfringens*, *Clostridium ramosum*, *Clostridium sordellii*, and *Clostridium sporogenes*.

^eTwo *Bacteroides ovatus*, two *Bacteroides vulgatus*, one *Bacteroides bivius* and one *Bacteroides disiens*.

lower airways (e.g. *Haemophilus* spp., *M. catarrhalis* and *S. pneumoniae*) have become more resistant to antibiotics widely used against these infections (e.g. macrolides, aminopenicillins, tetracycline and co-trimoxazole).¹⁴ Hence quinolones are an important option for therapy of respiratory tract infections. All of the quinolones included were highly active against these pathogens and inhibited 90% of *Haemophilus* spp. and *M. catarrhalis* at concentrations of between 0.004 and 0.06 mg/L. Clinafloxacin was the most active (MIC₉₀s = 0.004–0.008 mg/L), while Bay 12-

8039 and levofloxacin were the least active compounds (MIC₉₀s = 0.03–0.06 mg/L). To date, ciprofloxacin-resistant *Haemophilus influenzae* have been found only rarely.¹⁵ In contrast the MICs of quinolones for Gram-positive respiratory tract pathogens, e.g. *S. pneumoniae* or *S. aureus*, have increased markedly in Europe and the USA.^{16,17} Against *S. pneumoniae* Bay 12-8039 and trovafloxacin were the most active compounds (MIC₉₀s = 0.25 mg/L), while ciprofloxacin and levofloxacin were about eight times less active. Resistance to penicillins apparently did not

influence the susceptibility to quinolones of the *S. pneumoniae* isolates included.

From the results of this study the quinolones investigated may be classified by their activity against specific groups of pathogens. Against Gram-positive cocci, the highest, and about equal, activity was found for Bay 12-8039, clinafloxacin and trovafloxacin, while clinafloxacin was the most active compound against Enterobacteriaceae. Against *Pseudomonas* spp. clinafloxacin was the only compound with activity comparable to that of ciprofloxacin. Clinafloxacin was most active against fastidious organisms, while anaerobes, *H. pylori* and *C. jejuni* had lowest, and about equal, MICs of Bay 12-8039, gatifloxacin, clinafloxacin and trovafloxacin. A major breakthrough in quinolone antibacterial activity, e.g. against *P. aeruginosa* and *B. cepacia*, may require the introduction of novel structural elements.

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