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Antibacterial Spectrum of a Novel Des-Fluoro(6) Quinolone, BMS-284756

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The in vitro spectrum of a novel des-fluoro(6) quinolone, BMS-284756, was compared with those of five fluoroquinolones (trovafloxacin, moxifloxacin, levofloxacin, ofloxacin, and ciprofloxacin). BMS-284756 was among the most active and often was the most active quinolone against staphylococci (including methicillin-resistant strains), streptococci, pneumococci (including ciprofloxacin-nonsusceptible and penicillin-resistant strains), and *Enterococcus faecalis*. BMS-284756 inhibited ≈60 to ≈70% of the *Enterococcus faecium* (including vancomycin-resistant) strains and 90 to 100% of the *Enterobacteriaceae* strains and gastroenteric bacillary pathogens at the anticipated MIC susceptible breakpoint (≤4 μg/ml). Against the nonfermenters, BMS-284756 inhibited 90 to 100% of *Pseudomonas fluorescens*, *Pseudomonas stutzeri*, *Stenotrophomonas maltophilia*, *Flavobacterium* spp., and *Acinetobacter* spp. and 72% of *Pseudomonas aeruginosa* strains at 4 μg/ml. Against anaerobic bacteria, BMS-284756 was among the most active, inhibiting essentially all strains tested. It had very low MICs against the fastidious and atypical microbial species, in particular against mycoplasmas or ureaplasmas, *Borrelia burgdorferi*, chlamydia, and gonococci. These results indicate that with its broad antibacterial spectrum, BMS-284756 should be evaluated clinically for the treatment of community and nosocomial infections.

BMS-284756 is a novel des-fluoro(6) quinolone. This means that BMS-284756 differs from recently approved quinolones (i.e., the fluoroquinolones included in this study and gatifloxacin) in that BMS-284756 lacks a fluorine at the C-6 position. BMS-284756 (also known as T-3811ME) has antibacterial activity similar to those of fluorinated quinolones, but the des-F(6) derivatives are less acutely toxic in mice (K. Hayashi, Y. Todo, S. Hamamoto, K. Ojima, M. Yamada, T. Kito, M. Takahata, Y. Watanbe, and H. Narita, Abstr. 37th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-158, 1997).

Quinolones can differ in their antibacterial spectra and potencies. Notable potency differences among quinolones occur in their activities versus gram-positive bacteria, pseudomonads, anaerobic bacteria, and mycobacteria. In the present study, the antibacterial spectrum of BMS-284756 is compared to those of five fluoroquinolones against 1,150 strains representing 66 bacterial species. While the antibacterial activity of BMS-284756 was reported previously by Takahata et al. (9), the present study included additional bacterial species and was performed using NCCLS-recommended susceptibility test methods, whenever they were available for specific bacterial groups.

MATERIALS AND METHODS

Antimicrobial agents. BMS-284756 was obtained from Toyama Chemical Co. Ltd., Toyama, Japan, and moxifloxacin (MFX) and ciprofloxacin (CIP) were obtained from Bayer Corporation, West Haven, Conn. Levofloxacin (LVX) and trovafloxacin (TVA) were extracted and purified from commercially available tablets and were determined to be ≥95% pure by high-performance liquid chromatography. Ofloxacin (OFX) was purchased from Sigma Chemical Co., St. Louis, Mo.

Bacterial strains. All bacterial strains used in this study were clinical isolates obtained from numerous sources of broad geographical distribution. Isolates were maintained frozen in liquid nitrogen. Some of the quinolone-resistant *Neisseria gonorrhoeae* strains were provided by Ronald Jones (University of Iowa, Iowa City).

Methicillin-susceptible (MS) *Staphylococcus aureus* was defined as strains for which oxacillin MICs were ≤2 μg/ml, and MS strains of *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* were defined as strains for which oxacillin MICs were ≤0.25 μg/ml (4). Methicillin-resistant (MR) *S. aureus* strains were strains for which oxacillin MICs were ≥4 μg/ml, and MR *S. epidermidis* and *S. haemolyticus* strains were strains for which oxacillin MICs were ≥0.5 μg/ml. Because the oxacillin MIC interpretative breakpoint does not correlate with *mecA* carriage in *Staphylococcus saprophyticus* (2), MS and MR categorization in this species was based on *mecA* detection by PCR testing. All of the *S. saprophyticus* strains in this study were *mecA* negative.

Growth inhibitory activity. Determinations of the MICs for aerobic and anaerobic bacteria were performed by an agar dilution method in accordance with the procedure outlined by the NCCLS (4, 5). Other testing protocols used in this study were similar to those previously reported (1), with the following exceptions. Anaerobic bacterial susceptibility testing was done using brucella blood agar (5), *Chlamydia pneumoniae* with Hep-2 cells, and *Borrelia burgdorferi* with BSK H medium (Sigma).

The respective interpretative MIC breakpoints for strains susceptible, intermediate, and resistant to the quinolones are as follows: for TVA, ≤2, 4, and ≥8 μg/ml for general organisms (FDA-approved breakpoints), but ≤1, 2, and ≥4 μg/ml for *Streptococcus pneumoniae* and other streptococci (NCCLS-approved breakpoints), and ≤0.25 μg/ml for gonococci (susceptible breakpoint only); for MFX ≤2, 4, and ≥8 μg/ml for general organisms (FDA-approved breakpoints), but ≤1, 2, and ≥4 μg/ml for *Streptococcus pneumoniae*, with no interpretative MFX breakpoints for gonococci; for LVX and OFX, ≤2, 4, and ≥8 μg/ml for all organism groups (NCCLS-approved breakpoints), but for OFX only, ≤0.25, 0.5 to 1, and ≥2 μg/ml for gonococci; and for CIP, ≤1, 2, and ≥4 μg/ml for general organisms (NCCLS approved), with no interpretative criteria for *Streptococcus pneumoniae* and other streptococci, and ≤0.06, 0.12 to 0.5, and ≥1 μg/ml for gonococci (2).

The respective susceptible, intermediate, and resistant breakpoints used in the BMS-284756 clinical trials for this quinolone are ≤4, 8, and ≥16 μg/ml for the general organisms, ≤2, 4, and ≥8 μg/ml for MR *S. aureus*, and ≤2 (susceptible breakpoint only) for gonococci. The proposed ≤4-μg/ml susceptible breakpoint for BMS-284756 was based on a mean area under the curve (AUC) from 0 to infinity of 84.1 μg · h/ml following a single 400-mg oral dose of BMS-284756 (D. Gajjar, D. Grasela, A. Bello, Z. Ge, L. Christopher, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr 2259, 2000); this breakpoint is compared to the susceptible breakpoints of quinolones (TVA, MFX, LVX, and OFX) of ≤2 μg/ml and AUCs of 30 to 50 μg · h/ml (3a) following a single standard dose. For quinolones, the pharmacodynamic parameter most predictive of efficacy is the AUC/MIC ratio (6, 8). In this paper, ≤4 μg/ml was used as a point of reference in discussing the BMS-284756 MIC data.

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TABLE 1. In vitro antibacterial activities of BMS-284756 and five comparative quinolones

Organism (*n*)	Quinolone[a]	MIC (μg/ml)		
		Range	MIC_{50} (modal MIC)[b]	MIC_{90}
MS *Staphylococcus aureus* (27)	BMS	0.016–0.03	0.03	0.03
	TVA	0.016–0.06	0.03	0.06
	MFX	0.03–0.06	0.06	0.06
	LVX	0.12–0.25	0.25	0.25
	OFX	0.12–0.25	0.25	0.25
	CIP	0.12–0.5	0.25	0.5
MR *Staphylococcus aureus* (58)	BMS	0.016–2	0.03	2
	TVA	0.016–8	0.06	2
	MFX	0.03–4	0.06	2
	LVX	0.25–16	0.5	8
	OFX	0.25–>16	1	16
	CIP	0.25–>32	0.5	32
MS *Staphylococcus epidermidis* (10)	BMS	0.03–0.06	0.03	0.03
	TVA	0.03–0.06	0.06	0.06
	MFX	0.06–0.12	0.12	0.12
	LVX	0.12–0.25	0.25	0.25
	OFX	0.25–0.5	0.5	0.5
	CIP	0.12–0.5	0.25	0.5
MR *Staphylococcus epidermidis* (17)	BMS	0.016–2	0.03	2
	TVA	0.016–4	0.06	4
	MFX	0.03–2	0.06	2
	LVX	0.12–8	0.25	8
	OFX	0.12–32	0.5	16
	CIP	0.12–>64	0.25	64
MS *Staphylococcus haemolyticus* (10)	BMS	0.03–0.12	0.03	0.03
	TVA	0.03–0.12	0.06	0.06
	MFX	0.03–0.12	0.06	0.12
	LVX	0.12–0.25	0.12	0.25
	OFX	0.25–1	0.25	0.5
	CIP	0.25–0.5	0.25	0.25
MR *Staphylococcus haemolyticus* (18)	BMS	0.03–8	0.03	4
	TVA	0.03–16	0.06	16
	MFX	0.06–8	0.06	4
	LVX	0.12–32	0.25	16
	OFX	0.25–>32	1	>32
	CIP	0.25–>32	0.5	>32
mecA-negative *Staphylococcus saprophyticus* (15)	BMS	0.06	0.06	0.06
	TVA	0.06–0.12	0.12	0.12
	MFX	0.12	0.12	0.12
	LVX	0.25–0.5	0.5	0.5
	OFX	1	1	1
	CIP	0.5–1	0.5	0.5
Streptococcus pyogenes (10)	BMS	0.06–0.25	0.06	0.25
	TVA	0.03–0.12	0.06	0.12
	MFX	0.12–0.5	0.25	0.25
	LVX	0.25–1	0.5	1
	OFX	1–2	2	2
	CIP	0.5–1	0.5	1
Streptococcus agalactiae (10)	BMS	0.06–0.12	0.12	0.12
	TVA	0.12–0.25	0.12	0.25
	MFX	0.25	0.25	0.25
	LVX	1	1	1
	OFX	2–4	2	4
	CIP	1–2	2	2
Streptococcus groups C, G, and F (16)	BMS	0.06–0.25	0.12	0.25
	TVA	0.06–0.25	0.12	0.12
	MFX	0.12–0.5	0.25	0.25
	LVX	0.5–2	1	1
	OFX	2–4	2	2
	CIP	0.5–2	1	2
Streptococcus mitis (17)	BMS	0.06–0.25	0.12	0.25
	TVA	0.06–0.25	0.12	0.12
	MFX	0.12–0.5	0.25	0.5
	LVX	1–2	2	2
	OFX	1–4	2	4
	CIP	2–4	2	4
Streptococcus sanguis (18)	BMS	0.06–0.25	0.12	0.25
	TVA	0.06–0.25	0.12	0.25
	MFX	0.12–0.5	0.25	0.5
	LVX	1–2	2	2
	OFX	2–4	2	4
	CIP	1–4	2	4
Penicillin-susceptible *Streptococcus pneumoniae* (10)	BMS	0.06–0.12	0.12	0.12
	TVA	0.12–0.25	0.25	0.25
	MFX	0.12–0.25	0.25	0.25
	LVX	1–2	2	2
	OFX	2–4	2	4
	CIP	1–2	1	2
Penicillin-intermediate *Streptococcus pneumoniae* (10)	BMS	0.06–0.12	0.06	0.12
	TVA	0.12–0.25	0.12	0.25
	MFX	0.12–0.5	0.25	0.25
	LVX	1–2	1	2
	OFX	2–4	2	4
	CIP	1–4	2	2
Penicillin-resistant *Streptococcus pneumoniae* (10)	BMS	0.06–0.12	0.06	0.12
	TVA	0.06–0.25	0.12	0.25
	MFX	0.25–0.5	0.25	0.5
	LVX	1–2	1	2
	OFX	2–4	2	4
	CIP	1–8	1	2
Streptococcus pneumoniae strains for which the CIP MIC is ≥2 μg/ml (13)	BMS	0.12–2	0.12	0.5
	TVA	0.25–16	0.25	4
	MFX	0.25–8	0.25	2
	LVX	1–32	2	8
	OFX	2–64	4	16
	CIP	2–64	4	16
Enterococcus faecalis (18)	BMS	0.25–2	0.25	0.5
	TVA	0.25–8	0.5	0.5
	MFX	0.25–8	0.25	0.5
	LVX	1–32	1	2
	OFX	2–>32	4	8
	CIP	1–>32	2	2
Enterococcus faecium (13)	BMS	0.06–8	4	8
	TVA	0.06–8	0.5	4
	MFX	0.12–16	1	4
	LVX	0.5–32	2	4
	OFX	0.5–>32	4	16
	CIP	0.12–>32	2	8
VanA + VanB *Enterococcus* spp. (11)[c]	BMS	0.25–32	4	8
	TVA	0.25–16	2	8
	MFX	0.25–32	2	8
	LVX	1–64	2	32
	OFX	2–>64	8	64
	CIP	1–>64	4	>64
VanC *Enterococcus* spp. (8)[d]	BMS	0.25–0.5	(0.25)	
	TVA	0.25–2	(0.25–0.5)	
	MFX	0.25–1	(0.25–0.5)	
	LVX	1–4	(2)	
	OFX	2–8	(4)	
	CIP	0.25–4	(1)	
Listeria monocytogenes (17)	BMS	0.25–0.5	0.5	0.5
	TVA	0.12–0.25	0.25	0.25
	MFX	0.25–0.5	0.5	0.5
	LVX	1	1	1
	OFX	1–2	2	2
	CIP	1–2	1	1

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TABLE 1—*Continued*

Organism (*n*)	Quinolone[a]	MIC (μg/ml) Range	MIC_{50} (modal MIC)[b]	MIC_{90}
Escherichia coli (18)	BMS	0.03–0.06	0.06	0.06
	TVA	0.03–0.06	0.03	0.06
	MFX	0.03–0.12	0.06	0.06
	LVX	0.016–0.06	0.03	0.06
	OFX	0.016–0.06	0.06	0.06
	CIP	0.004–0.03	0.016	0.016
Klebsiella pneumoniae (18)	BMS	0.12–1	0.25	0.5
	TVA	0.06–0.5	0.12	0.5
	MFX	0.12–1	0.12	0.5
	LVX	0.03–0.25	0.06	0.25
	OFX	0.03–1	0.12	0.5
	CIP	0.016–0.25	0.03	0.25
Klebsiella oxytoca (18)	BMS	0.06–0.25	0.12	0.25
	TVA	0.03–0.12	0.06	0.12
	MFX	0.03–0.25	0.12	0.12
	LVX	0.03–0.12	0.03	0.06
	OFX	0.03–0.25	0.06	0.12
	CIP	0.008–0.06	0.016	0.03
Enterobacter cloacae (18)	BMS	0.06–0.5	0.12	0.5
	TVA	0.06–0.5	0.12	0.5
	MFX	0.06–0.5	0.06	0.25
	LVX	0.03–0.25	0.03	0.12
	OFX	0.06–1	0.06	0.12
	CIP	0.008–0.25	0.016	0.03
Enterobacter aerogenes (17)	BMS	0.03–1	0.12	0.25
	TVA	0.03–0.5	0.06	0.12
	MFX	0.03–1	0.12	0.25
	LVX	0.03–0.5	0.06	0.12
	OFX	0.06–1	0.06	0.12
	CIP	0.008–0.25	0.016	0.06
Citrobacter freundii (18)	BMS	0.06–4	0.12	2
	TVA	0.03–4	0.06	1
	MFX	0.06–8	0.12	1
	LVX	0.03–2	0.03	1
	OFX	0.06–4	0.06	1
	CIP	0.004–2	0.016	0.25
Citrobacter koseri (18)	BMS	0.03–0.5	0.03	0.25
	TVA	0.016–0.5	0.03	0.25
	MFX	0.03–0.5	0.03	0.25
	LVX	0.03–0.5	0.03	0.06
	OFX	0.03–1	0.06	0.25
	CIP	0.004–0.5	0.008	0.06
Serratia marcescens (18)	BMS	0.25–2	1	2
	TVA	0.12–1	0.5	0.5
	MFX	0.06–1	0.25	0.5
	LVX	0.06–0.5	0.12	0.25
	OFX	0.12–2	0.5	1
	CIP	0.06–1	0.25	0.5
Proteus mirabilis (18)	BMS	0.25–1	0.5	1
	TVA	0.25–1	0.5	1
	MFX	0.25–1	0.5	1
	LVX	0.06–0.25	0.12	0.25
	OFX	0.25–0.5	0.25	0.5
	CIP	0.06–0.25	0.12	0.12
Proteus vulgaris (18)	BMS	0.06–8	0.5	8
	TVA	0.06–2	0.5	1
	MFX	0.06–2	0.5	1
	LVX	0.03–0.25	0.06	0.25
	OFX	0.06–0.5	0.25	0.5
	CIP	0.016–0.12	0.06	0.12
Morganella morganii (18)	BMS	0.12–1	0.5	1
	TVA	0.12–0.5	0.25	0.5
	MFX	0.12–0.5	0.25	0.5
	LVX	0.03–0.12	0.03	0.25
	OFX	0.06–0.25	0.06	0.25
	CIP	0.008–0.06	0.016	0.06
Providencia stuartii (18)	BMS	0.12–8	0.25	2
	TVA	0.12–4	0.25	1
	MFX	0.25–8	0.25	2
	LVX	0.12–8	0.12	8
	OFX	0.06–>16	0.12	>16
	CIP	0.25–>16	0.5	16
Providencia rettgeri (17)	BMS	0.06–2	0.5	2
	TVA	0.06–2	0.25	2
	MFX	0.06–2	0.5	2
	LVX	0.016–2	0.25	1
	OFX	0.008–4	0.12	2
	CIP	0.03–4	0.5	4
Salmonella spp. (18)	BMS	0.008–0.25	0.06	0.12
	TVA	0.016–0.25	0.06	0.12
	MFX	0.03–0.25	0.12	0.25
	LVX	0.06–0.5	0.25	0.25
	OFX	0.03–0.25	0.12	0.12
	CIP	0.008–0.03	0.016	0.03
Shigella spp. (18)	BMS	≤0.001–0.06	0.03	0.03
	TVA	0.004–0.06	0.03	0.03
	MFX	0.004–0.06	0.06	0.06
	LVX	0.008–0.03	0.03	0.03
	OFX	0.016–0.06	0.06	0.06
	CIP	0.004–0.03	0.016	0.03
Yersinia enterocolitica (13)	BMS	0.03–0.06	0.06	0.06
	TVA	0.03–0.12	0.06	0.06
	MFX	0.06–0.12	0.06	0.12
	LVX	0.016–0.06	0.03	0.06
	OFX	0.03–0.12	0.06	0.12
	CIP	0.004–0.03	0.03	0.03
Aeromonas hydrophila (16)	BMS	0.06–1	0.12	0.5
	TVA	0.03–0.25	0.03	0.12
	MFX	0.016–0.12	0.03	0.12
	LVX	0.008–0.03	0.008	0.03
	OFX	0.008–0.06	0.016	0.06
	CIP	0.002–0.016	0.004	0.016
Vibrio cholerae (13)	BMS	0.001–0.25	0.004	0.008
	TVA	0.004–0.12	0.004	0.008
	MFX	0.008–0.12	0.016	0.03
	LVX	0.004–0.12	0.008	0.008
	OFX	0.008–0.12	0.008	0.016
	CIP	0.002–0.004	0.002	0.004
Campylobacter jejuni (12)	BMS	0.06–0.25	0.12	0.12
	TVA	0.008–0.03	0.016	0.03
	MFX	0.03–0.12	0.06	0.06
	LVX	0.06–0.12	0.06	0.12
	OFX	0.12–0.5	0.25	0.25
	CIP	0.06–0.25	0.12	0.12
Pseudomonas aeruginosa (18)	BMS	2–32	4	16
	TVA	1–4	1	4
	MFX	2–16	4	8
	LVX	0.5–4	1	4
	OFX	1–8	2	4
	CIP	0.25–2	0.5	2
Pseudomonas fluorescens (15)	BMS	0.5–8	1	8
	TVA	0.12–4	0.5	4
	MFX	0.25–16	1	16
	LVX	0.12–2	0.25	2
	OFX	0.25–8	0.5	8
	CIP	0.06–2	0.12	1
Pseudomonas stutzeri (15)	BMS	0.03–1	0.5	1
	TVA	0.12–0.5	0.12	0.5
	MFX	0.03–1	0.25	1
	LVX	0.016–0.25	0.06	0.25
	OFX	0.03–0.5	0.12	0.25
	CIP	0.016–0.12	0.06	0.12

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TABLE 1—*Continued*

Organism (*n*)	Quinolone[a]	MIC (μg/ml)		
		Range	MIC_{50} (modal MIC)[b]	MIC_{90}
Burkholderia cepacia (18)	BMS	4–32	8	16
	TVA	1–4	2	4
	MFX	2–8	2	4
	LVX	2–8	2	4
	OFX	4–8	8	8
	CIP	2–16	4	8
Stenotrophomonas maltophilia (18)	BMS	0.25–8	2	4
	TVA	0.12–4	0.5	1
	MFX	0.12–4	0.5	1
	LVX	0.25–8	0.5	2
	OFX	1–8	2	8
	CIP	1–32	4	8
Flavobacterium spp. (17)	BMS	0.016–0.5	0.25	0.5
	TVA	0.03–0.25	0.12	0.25
	MFX	0.06–1	0.25	0.5
	LVX	0.12–2	0.5	2
	OFX	0.25–4	2	4
	CIP	0.25–4	1	4
Acinetobacter baumannii (18)	BMS	0.03–2	0.06	0.25
	TVA	0.016–1	0.03	0.25
	MFX	0.06–2	0.12	1
	LVX	0.06–4	0.12	1
	OFX	0.25–8	0.5	2
	CIP	0.25–8	0.5	2
Acinetobacter lwoffii (18)	BMS	0.03–0.25	0.06	0.12
	TVA	0.016–0.12	0.03	0.06
	MFX	0.03–1	0.06	0.25
	LVX	0.06–1	0.12	0.25
	OFX	0.12–2	0.25	1
	CIP	0.12–2	0.25	1
Alcaligenes spp. (18)	BMS	1–16	8	16
	TVA	0.25–16	2	8
	MFX	0.12–4	2	2
	LVX	0.06–2	1	2
	OFX	0.12–4	1	4
	CIP	0.12–4	2	4
Bacteroides fragilis (18)	BMS	0.12–1	0.25	0.5
	TVA	0.25–0.5	0.25	0.5
	MFX	0.25–1	0.25	0.5
	LVX	1–4	1	2
	OFX	2–8	2	4
	CIP	2–64	4	8
Bacteroides thetaiotaomicron (11)	BMS	0.03–1	0.5	0.5
	TVA	0.12–1	1	1
	MFX	0.12–2	2	2
	LVX	0.25–8	4	8
	OFX	0.5–16	16	16
	CIP	1–16	16	16
Fusobacterium spp. (13)	BMS	0.03–2	0.5	2
	TVA	0.12–4	1	4
	MFX	0.25–4	2	4
	LVX	0.25–4	2	4
	OFX	0.5–16	8	8
	CIP	0.25–8	2	8
Clostridium perfringens (18)	BMS	0.5–1	1	1
	TVA	0.25–0.5	0.25	0.5
	MFX	0.5	0.5	0.5
	LVX	0.5–1	0.5	1
	OFX	1	1	1
	CIP	0.5–2	1	1
Clostridium difficile (25)	BMS	0.25–2	0.5	1
	TVA	0.25–2	1	1
	MFX	0.5–1	1	1
	LVX	0.5–4	4	4
	OFX	1–8	8	8
	CIP	1–16	8	16
Peptostreptococcus spp. (17)	BMS	0.03–16	0.25	0.25
	TVA	0.016–8	0.25	1
	MFX	0.03–2	0.25	1
	LVX	0.12–16	0.5	4
	OFX	0.25–32	1	8
	CIP	0.12–8	0.5	2
Propionibacterium acnes (17)	BMS	0.25–0.5	0.25	0.5
	TVA	0.5–1	0.5	1
	MFX	0.25	0.25	0.25
	LVX	0.25–0.5	0.5	0.5
	OFX	0.5–1	0.5	1
	CIP	0.25–0.5	0.5	0.5
CIP-susceptible *Neisseria gonorrhoeae* (35)	BMS	0.001–0.03	0.004	0.008
	TVA	≤0.0005	<0.0005	<0.0005
	MFX	0.004–0.06	0.008	0.03
	LVX	0.008–0.03	0.008	0.016
	OFX	0.016–0.12	0.016	0.03
	CIP	0.002–0.016	0.004	0.008
CIP-nonsusceptible *Neisseria gonorrhoeae* (10)	BMS	0.06–0.5	0.25	0.25
	TVA	0.03–1	0.12	0.5
	MFX	0.12–1	0.25	1
	LVX	0.12–2	0.5	2
	OFX	0.25–2	1	2
	CIP	0.12–2	0.5	1
Neisseria meningitidis (17)	BMS	0.008–0.016	0.008	0.008
	TVA	0.004	0.004	0.004
	MFX	0.008–0.016	0.016	0.016
	LVX	0.016	0.016	0.016
	OFX	0.016–0.03	0.016	0.03
	CIP	0.004–0.008	0.004	0.008
Gardnerella vaginalis (12)	BMS	0.25–0.5	0.5	0.5
	TVA	0.5–2	1	1
	MFX	0.25–0.5	0.5	0.5
	LVX	0.5–1	1	1
	OFX	0.5–2	1	2
	CIP	0.5–2	1	2
Haemophilus influenzae (35)	BMS	0.004–0.03	0.016	0.03
	TVA	0.004–0.03	0.008	0.016
	MFX	0.016–0.06	0.03	0.06
	LVX	0.016–0.03	0.03	0.03
	OFX	0.03–0.06	0.06	0.06
	CIP	0.016–0.03	0.016	0.03
Moraxella catarrhalis (10)	BMS	0.008–0.03	0.03	0.03
	TVA	0.016–0.03	0.03	0.03
	MFX	0.06–0.12	0.12	0.12
	LVX	0.03–0.06	0.06	0.06
	OFX	0.12	0.12	0.12
	CIP	0.03–0.06	0.06	0.06
Bordetella spp. (14)	BMS	0.06–0.25	0.06	0.25
	TVA	0.03–0.25	0.06	0.25
	MFX	0.06	0.06	0.06
	LVX	0.06–0.12	0.06	0.06
	OFX	0.12	0.12	0.12
	CIP	0.12	0.12	0.12
Borellia burgdorferi (6)[e]	BMS	0.06–0.5	(0.25)	
	TVA	0.5–2	(0.5–2)	
	MFX	2–8	(4)	
	LVX	4–16	(4)	
	OFX	2–4	(4)	
	CIP	2–4	(4)	
Helicobacter pylori (10)	BMS	0.03–0.12	0.06	0.06
	TVA	0.03–0.25	0.06	0.25
	MFX	0.12–0.5	0.25	0.5
	LVX	0.12–0.25	0.12	0.25
	OFX	0.06–0.25	0.12	0.12
	CIP	0.016–0.06	0.03	0.06

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TABLE 1—*Continued*

Organism (*n*)	Quinolone[a]	MIC (μg/ml)		
		Range	MIC_{50} (modal MIC)[b]	MIC_{90}
Bartonella spp. (3)	BMS	0.5–1	(1)	
	TVA	0.5–1	(0.5)	
	MFX	0.5–1	(1)	
	LVX	1–2	(1)	
	OFX	2–4	(2)	
	CIP	1–2	(1)	
Legionella spp. (25)	BMS	0.008–0.12	0.016	0.06
	TVA	0.001–0.03	0.004	0.016
	MFX	0.016–0.25	0.03	0.06
	LVX	0.008–1	0.016	0.03
	OFX	0.06–0.12	0.06	0.12
	CIP	0.03–0.12	0.03	0.06
Mycoplasma pneumoniae (11)	BMS	0.03–0.12	0.03	0.06
	TVA	0.12–0.5	0.25	0.25
	MFX	0.06–0.25	0.12	0.12
	LVX	0.25–1	0.5	0.5
	OFX	1–2	1	1
	CIP	1–2	1	2
Mycoplasma hominis (11)	BMS	0.008–0.25	0.03	0.03
	TVA	0.016–0.12	0.03	0.06
	MFX	0.03–0.12	0.06	0.12
	LVX	0.25–4	1	2
	OFX	0.5–8	2	8
	CIP	0.5–4	1	2
Ureaplasma urealyticum (11)	BMS	0.12–1	0.12	0.25
	TVA	0.12–0.5	0.5	0.5
	MFX	0.25–1	0.5	1
	LVX	0.5–4	1	4
	OFX	2–4	4	4
	CIP	4–16	8	8
Mycobacterium tuberculosis (10)	BMS	0.03–2	2	2
	MFX	0.03–0.25	0.06	0.12
	LVX	0.12–1	0.5	1
	OFX	0.5–2	2	2
	CIP	1–4	1	4
Mycobacterium avium-Mycobacterium intracellulare (6)	BMS	0.5–8	(2)	
	MFX	0.12–0.5	(0.5)	
	LVX	0.5–2	(1)	
	OFX	8–>16	(>16)	
	CIP	8–>16	(8, >16)	
Chlamydia trachomatis (10)	BMS	≤0.004–0.016	0.008	0.016
	MFX	0.03–0.06	0.03	0.06
	LVX	0.25–0.5	0.25	0.5
	OFX	1–2	1	2
	CIP	0.25–2	1	2
Chlamydia pneumoniae (4)	BMS	≤0.004–0.008	(0.008)	
	MFX	0.06–0.12	(0.06)	
	LVX	0.5	(0.5)	
	OFX	0.5–1	(1)	
	CIP	0.5	(0.5)	

[a] BMS, BMS-284756.
[b] Modal MICs are listed in parentheses if the number of strains tested was <10.
[c] Includes seven VanA (two *E. faecalis* and five *E. faecium*) and four VanB (two *E. faecalis* and two *E. faecium*) strains.
[d] Includes four strains each of *E. gallinarum* and *E. casseliflavus*.
[e] Only three of the six strains were tested with OFX.

RESULTS AND DISCUSSION

All of the results discussed in this section are listed in Table 1.

Gram-positive aerobic bacteria. BMS-284756 was the most active quinolone against MS and MR staphylococci. BMS-284756 was generally 2-fold more active than TVA and MFX and 8- to 32-fold more active than LVX, OFX, and CIP. The quinolones inhibited MS staphylococci uniformly, with MICs at which 50% of the isolated were inhibited (MIC_{50}s) and MIC_{90}s generally being equal. By comparison, the quinolone MIC ranges were broader for MR staphylococci, with MIC_{50}s and MIC_{90}s differing by 32- to 64-fold. The fact that quinolone resistance is more commonly encountered among MR than MS staphylococcal clinical isolates accounts for the higher quinolone MIC_{90}s for MR strains (3, 7). In fact, for 40 to 50% of MR strains tested, CIP MICs were ≥2 μg/ml, compared with 0% of MS strains. For all the MR *S. aureus* strains, BMS-284756 MICs were ≤2 μg/ml.

The quinolones can be grouped by their streptococcal and pneumococcal potencies. BMS-284756, TVA, and MFX were about 10-fold more active than LVX, OFX, and CIP against these organisms. Along with BMS-284756 (MIC_{90}s = 0.12 to 0.25 μg/ml), LVX, TVA, and MFX covered all the streptococci and pneumococci at their susceptible breakpoints, but only BMS-284756 covered all *Streptococcus pneumoniae* strains with CIP MICs of ≥2 μg/ml (85% of which had OFX MICs of ≥4 μg/ml), and for 90% of the latter isolates BMS-284756 MICs were ≤0.5 μg/ml. As with streptococci, the enterococci were more susceptible to BMS-284756, TVA, and MFX than to LVX, OFX, and CIP. The quinolones were more active against *Enterococcus faecalis* than to *Enterococcus faecium*, the latter being more frequently resistant to quinolones. While BMS-284756, TVA, MFX, and LVX covered ≈90% or more of the *E. faecalis* and VanC enterococcal species (i.e., *Enterococcus gallinarum* and *Enterococcus casseliflavus*), only BMS-284756 covered >50% of *E. faecium* and VanA and VanB strains (comprised primarily of *E. faecium*) at ≤4 μg/ml.

Gram-negative aerobic bacteria. The quinolones have good activities against *Enterobacteriaceae*. Overall, CIP was the most active against *Enterobacteriaceae*, except *Providencia* spp. BMS-284756 was less active against the *Enterobacteriaceae*, but for almost all of the *Enterobacteriaceae* strains, BMS-284756 MICs were ≤4 μg/ml, levels that are achievable in plasma for this quinolone.

For bacterial species associated with gastroenteritis (*Salmonella* spp., *Shigella* spp., *Yersinia enterocolitica*, *Aeromonas hydrophila*, *Vibrio cholerae*, and *Campylobacter jejuni*), all the quinolones showed potent and generally similar activities.

Nonfermentative bacteria. Pseudomonal susceptibility to the quinolones is species dependent. Against *Pseudomonas aeruginosa*, CIP remained the most active. Approximately 90% of the *P. aeruginosa* strains were susceptible to CIP, TVA, and LVX, 72% were susceptible to OFX and BMS-284756 (at ≤4 μg/ml), and 28% were susceptible to MFX. All *Pseudomonas stutzeri* strains were susceptible to the six quinolones tested. All of the *Pseudomonas fluorescens* strains were susceptible to LVX, compared to the 87 to 93% of strains that were susceptible to CIP, TVA MFX, and BMS-284756 (at ≤4 μg/ml) and 67% that were susceptible to OFX.

In contrast, CIP was among the least active quinolones against the pseudomonas-related species, being inactive against *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and other nonfermenters (*Flavobacterium* and *Acinetobacter* spp.). While BMS-284756 MIC_{90}s for *Stenotrophomonas maltophilia*, *Flavobacterium* spp., and *Acinetobacter* spp. were ≤4 μg/ml, *Burkholderia cepacia* and *Alcaligenes* spp. were generally resistant.

Anaerobic bacteria. The broadest antianaerobic bacterial spectra were observed with BMS-284756, TVA, and MFX. BMS-284756 was very active against anaerobic bacteria, inhibiting all but one peptostreptococcal strain at 4 μg/ml.

Fastidious bacterial species. BMS-284756's exceptional antigonococcal activity extended to all CIP-nonsusceptible strains. Though the quinolones inhibited all CIP-susceptible *N. gonorrhoeae* strains, the BMS-284756 MIC_{90} for CIP-nonsusceptible isolates was ≤0.25 μg/ml. While TVA was 10-fold more active than BMS-284756 against CIP-susceptible gonococci, the BMS-284756 MIC_{90} for CIP-nonsusceptible strains was 2-fold better than that of TVA.

The quinolones were very active (MIC_{90}s, ≤0.1 μg/ml) against *Neisseria meningitidis*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Legionella* spp., with good activities (MIC_{90}s, ≤0.5 μg/ml) also against *Bordetella* spp. and *Helicobacter pylori*. Included in the quinolones' spectra were all strains of *Gardnerella vaginalis* (except CIP), *Mycoplasma pneumoniae* (except CIP), and *Bartonella* spp. (except CIP and OFX). Only BMS-284756 and TVA inhibited all *B. burgdorferi* strains, with BMS-284756 MICs being 16-fold better than those of MFX, LVX, OFX, and CIP against the Lyme disease spirochete. BMS-284756, TVA, and MFX inhibited all *Mycoplasma hominis* and *Ureaplasma urealyticum* strains tested, with MIC_{90}s 10- to 100-fold better than those of LVX, OFX, and CIP against *M. hominis* and up to 30-fold better against *U. urealyticum*. This des-F(6) quinolone was the most active against chlamydia, with all strains being inhibited at ≤0.016 μg/ml; BMS-284756 was 100- to 1,000-fold more active than OFX and CIP, 50-fold more potent than LVX, and 10- to 50-fold better than MFX against chlamydia.

Of the quinolones tested, MFX was the most active against mycobacteria and CIP was the least active. BMS-284756 was comparable to OFX (MIC_{90}, 2 μg/ml) against *Mycobacterium tuberculosis*. BMS-284756 was previously reported to have good antitubercular activity, with a MIC_{90} of 0.06 μg/ml (9). In the present study, the MIC_{90} of BMS-284756 against *M. tuberculosis* was 2 μg/ml. The difference in these MIC_{90} results against *M. tuberculosis* is likely due to susceptibility test differences. A broth macrodilution method was used in this study, whereas Takahata et al. (9) used a broth microdilution assay. Nevertheless, both studies concluded that the antitubercular activities of BMS-284756 and OFX are comparable. A recent study (E. J. Alvirez-Froitex and M. H. Cynamon, 9th Int. Congr. Infect. Dis., Abstr. 75.015, 2000), testing seven *M. tuberculosis* strains by a broth macrodilution test, yielded modal MICs of 1 μg/ml for BMS-284756 versus 0.5 and 0.06 μg/ml for LVX and MFX, respectively.

In summary, BMS-284756 is among the most active quinolones tested against gram-positive bacteria, particularly against MR *S. aureus*, *S. epidermidis*, and CIP-resistant *S. pneumoniae*. BMS-284756 had the broadest antianaerobic bacterial coverage, inhibiting almost all of the anaerobic bacterial strains tested. BMS-284756 was the most active quinolone against fastidious microbes (mycoplasmas, ureaplasmas, chlamydiae, CIP-nonsusceptible gonococci, and *B. burgdorferi*). It is active against the *Enterobacteriaceae* and most nonfermenters. The wide antibacterial spectrum of BMS-284756 supports its development for a broad range of indications.

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