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In Vitro and Bactericidal Activities of ABT-492, a Novel Fluoroquinolone, against Gram-Positive and Gram-Negative Organisms

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In vitro activities of ABT-492, ciprofloxacin, levofloxacin, trovafloxacin, moxifloxacin, gatifloxacin, and gemifloxacin were compared. ABT-492 was more potent against quinolone-susceptible and -resistant gram-positive organisms, had activity similar to that of ciprofloxacin against certain members of the family *Enterobacteriaceae*, and had comparable activity against quinolone-susceptible, nonfermentative, gram-negative organisms. Bactericidal activity of ABT-492 was also evaluated.

Antimicrobial resistance continues to be problematic. Resistance rates in other U.S. studies were examined. More than 30% of *Streptococcus pneumoniae* clinical isolates are penicillin nonsusceptible, and approximately 25% are macrolide resistant (7, 10). In *Haemophilus influenzae*, β-lactamase-mediated ampicillin resistance is about 28% (11). In uncomplicated urinary tract infections, 10 to 20% of *Escherichia coli* isolates are resistant to trimethoprim-sulfamethoxazole and 33 to 40% are resistant to ampicillin (8, 13). Methicillin resistance in nosocomial *Staphylococcus aureus* has increased from 2.1% to 26–44%, and methicillin-resistant *S. aureus* (MRSA) is becoming a problem in community-acquired infections (1, 9, 22, 23).

Fluoroquinolones have broad-spectrum activity. Newer quinolones demonstrate increased potency against *S. pneumoniae*, staphylococci, *H. influenzae*, and some enterococci and have a potency equivalent to that of ciprofloxacin against members of the family *Enterobacteriaceae* (3, 5, 12, 15, 16). In the United States, quinolone resistance remains low in *S. pneumoniae* and has been reported only rarely in *H. influenzae* (2, 6, 14, 25).

ABT-492 is a new fluoroquinolone with increased activity, compared to levofloxacin, trovafloxacin, and ciprofloxacin, against gram-positive organisms and activity similar to that of ciprofloxacin against certain gram-negative, quinolone-susceptible and -resistant organisms (20). The in vitro activities of ABT-492, moxifloxacin, gatifloxacin, gemifloxacin, levofloxacin, trovafloxacin, and ciprofloxacin were evaluated against 919 quinolone-susceptible and -resistant gram-positive and gram-negative pathogens. MIC ranges and MICs inhibiting 50% (MIC_{50}) and 90% (MIC_{90}) of the tested strains are shown in Table 1. Time-kill analyses of ABT-492, ciprofloxacin, and moxifloxacin were also performed.

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Clinical isolates dating from 1983 to 2000 from the Abbott culture collection and reference strains from the American Type Culture Collection (Manassas, Va.) were tested. Strains were classified as quinolone susceptible or resistant on the basis of levofloxacin or ciprofloxacin susceptibility for gram-positive and gram-negative organisms, respectively, according to the interpretive criteria of the National Committee for Clinical Laboratory Standards (NCCLS) (17).

ABT-492 and comparator quinolones were synthesized at Abbott Laboratories (Abbott Park, Ill.). Penicillin and oxacillin were purchased from Sigma Chemical Company (St. Louis, Mo.).

MIC determinations and quality control tests were performed by the NCCLS broth microdilution method and interpreted according to NCCLS-defined breakpoints (17, 18).

The molecular mechanisms of quinolone resistance were identified by PCR amplification and DNA sequence analysis of the *gyrA* and *grlA*/*parC* genes for the *S. aureus*, *S. pneumoniae*, and *E. coli* strains used in time-kill studies (1, 4, 21, 26).

Kill kinetics of selected quinolone-susceptible and -resistant strains of *S. aureus*, *S. pneumoniae*, *E. coli*, and *Pseudomonas aeruginosa* were determined by NCCLS methods at four and eight times the MICs of ABT-492, ciprofloxacin, and moxifloxacin (19). Starting MICs were determined by the NCCLS broth microdilution method (18). Colony counts were performed. To determine if there were antibiotic carryover effects of ABT-492, ciprofloxacin, and moxifloxacin, experiments were performed as previously described (19, 24). No antibiotic carryover effects of ABT-492 and ciprofloxacin were observed. For quinolone-susceptible *P. aeruginosa*, there was a 10-fold decrease in the number of CFU per milliliter in the moxifloxacin plate counts at eight times the MIC when bacteria were plated immediately compared to the control (no drug), which was reproducible upon additional testing, suggesting a possible antibiotic carryover effect for this strain only. The kill kinetic for this strain showed that all three quinolones were rapidly bactericidal.

ABT-492 and gemifloxacin were the most potent quinolones against quinolone-susceptible and -resistant gram-positive organisms. ABT-492 MIC_{90}s were 0.008 to 1 μg/ml for quino-

TABLE 1. Comparative in vitro activities of ABT-492 against gram-positive and gram-negative organisms

Strain	No. of isolates	Antibiotic	MIC (μg/ml)		
			Range	50% of strains	90% of strains
S. pneumoniae (levofloxacin resistant)	33	ABT-492	0.015–0.5	0.12	0.5
		Levofloxacin	2–32	16	32
		Trovafloxacin	0.25–8	2	4
		Ciprofloxacin	4–64	32	64
		Moxifloxacin	0.25–8	2	4
		Gatifloxacin	0.5–8	4	8
		Gemifloxacin	0.06–2	0.25	1
S. pneumoniae (levofloxacin susceptible)	69	ABT-492	0.004–0.015	0.008	0.015
		Levofloxacin	0.5–2	1	1
		Trovafloxacin	0.03–0.25	0.06	0.12
		Ciprofloxacin	0.5–4	1	2
		Moxifloxacin	0.06–0.25	0.12	0.12
		Gatifloxacin	0.06–0.5	0.25	0.25
		Gemifloxacin	0.008–0.06	0.03	0.03
S. pyogenes (levofloxacin susceptible)	50	ABT-492	0.001–0.03	0.008	0.015
		Levofloxacin	0.25–2	0.5	1
		Trovafloxacin	0.03–1	0.06	0.12
		Ciprofloxacin	0.12–4	0.5	1
		Moxifloxacin	0.03–0.5	0.12	0.25
		Gatifloxacin	0.06–0.5	0.25	0.5
		Gemifloxacin	0.004–0.06	0.015	0.06
S. aureus (levofloxacin resistant)	71	ABT-492	0.015–1	0.25	1
		Levofloxacin	4–64	16	32
		Trovafloxacin	0.5–16	2	8
		Ciprofloxacin	4–>128	64	128
		Moxifloxacin	0.25–16	4	8
		Gatifloxacin	0.5–16	8	16
		Gemifloxacin	0.25–32	4	16
S. aureus (levofloxacin susceptible)	70	ABT-492	0.002–0.008	0.004	0.008
		Levofloxacin	0.06–0.5	0.25	0.5
		Trovafloxacin	0.008–0.12	0.03	0.06
		Ciprofloxacin	0.12–1	0.5	1
		Moxifloxacin	0.015–0.5	0.06	0.12
		Gatifloxacin	0.03–0.25	0.12	0.12
		Gemifloxacin	0.008–0.12	0.03	0.06
S. epidermidis (levofloxacin resistant)	10	ABT-492	0.12–1	0.5	0.5
		Levofloxacin	4–128	16	16
		Trovafloxacin	1–32	4	4
		Ciprofloxacin	4–>128	32	32
		Moxifloxacin	1–>128	2	2
		Gatifloxacin	1–32	2	2
		Gemifloxacin	0.5–8	4	4
S. epidermidis (levofloxacin susceptible)	9	ABT-492	0.002–0.008	NA[a]	0.008
		Levofloxacin	0.12–0.5	NA	0.25
		Trovafloxacin	0.03–0.25	NA	0.12
		Ciprofloxacin	0.12–0.5	NA	0.25
		Moxifloxacin	0.03–0.12	NA	0.12
		Gatifloxacin	0.06–0.12	NA	0.12
		Gemifloxacin	0.015–0.06	NA	0.06
E. faecalis (levofloxacin resistant)	26	ABT-492	0.06–32	0.25	8
		Levofloxacin	16–128	32	128
		Trovafloxacin	1–16	8	16
		Ciprofloxacin	8–>128	128	128
		Moxifloxacin	2–64	8	32
		Gatifloxacin	4–64	16	64
		Gemifloxacin	0.25–64	4	32
		Vancomycin	0.25–>128	0.5	16

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TABLE 1—*Continued*

Strain	No. of isolates	Antibiotic	MIC (μg/ml)		
			Range	50% of strains	90% of strains
E. faecalis (levofloxacin susceptible)	18	ABT-492	0.03–0.12	0.06	0.06
		Levofloxacin	0.5–2	1	1
		Trovafloxacin	0.06–0.5	0.12	0.25
		Ciprofloxacin	0.25–2	1	1
		Moxifloxacin	0.12–0.5	0.25	0.5
		Gatifloxacin	0.25–1	0.5	0.5
		Gemifloxacin	0.03–0.25	0.06	0.25
		Vancomycin	0.25–2	0.5	1
E. faecium (levofloxacin resistant)	28	ABT-492	0.25–16	4	8
		Levofloxacin	8–>128	32	64
		Trovafloxacin	2–32	8	16
		Ciprofloxacin	8–128	128	128
		Moxifloxacin	1–32	16	16
		Gatifloxacin	4–64	16	32
		Gemifloxacin	1–32	16	32
		Vancomycin	2–>128	>128	>128
E. faecium (levofloxacin susceptible)	14	ABT-492	0.06–2	0.12	1
		Levofloxacin	0.5–4	1	4
		Trovafloxacin	0.06–2	0.5	1
		Ciprofloxacin	0.5–8	2	4
		Moxifloxacin	0.12–4	1	2
		Gatifloxacin	0.25–4	1	2
		Gemifloxacin	0.03–4	0.25	2
		Vancomycin	0.5–>128	4	128
H. influenzae (ciprofloxacin resistant)	6	ABT-492	0.004–0.5	NA	NA
		Levofloxacin	0.06–8	NA	NA
		Trovafloxacin	0.12–16	NA	NA
		Ciprofloxacin	0.06–32	NA	NA
		Moxifloxacin	0.06–8	NA	NA
		Gatifloxacin	0.03–8	NA	NA
		Gemifloxacin	0.03–1	NA	NA
H. influenzae (ciprofloxacin susceptible)	110	ABT-492	≤0.00025–0.004	0.0005	0.002
		Levofloxacin	0.002–0.5	0.015	0.03
		Trovafloxacin	≤0.001–0.12	0.008	0.03
		Ciprofloxacin	0.002–0.5	0.015	0.015
		Moxifloxacin	0.004–0.12	0.015	0.06
		Gatifloxacin	0.002–0.03	0.008	0.03
		Gemifloxacin	≤0.001–0.06	0.004	0.015
M. catarrhalis (ciprofloxacin susceptible)	50	ABT-492	0.0005–0.03	0.002	0.004
		Levofloxacin	0.015–0.25	0.03	0.06
		Trovafloxacin	0.004–0.06	0.015	0.015
		Ciprofloxacin	0.008–0.25	0.03	0.06
		Moxifloxacin	0.03–0.12	0.06	0.06
		Gatifloxacin	0.015–0.12	0.03	0.06
		Gemifloxacin	0.004–0.06	0.015	0.015
E. coli (ciprofloxacin resistant)	27	ABT-492	1–16	4	8
		Levofloxacin	4–128	16	64
		Trovafloxacin	8–>128	64	>128
		Ciprofloxacin	4–>128	128	>128
		Moxifloxacin	8–>128	32	64
		Gatifloxacin	4–64	8	32
		Gemifloxacin	2–>128	32	128
E. coli (ciprofloxacin susceptible)	45	ABT-492	0.004–0.25	0.03	0.06
		Levofloxacin	0.015–0.25	0.03	0.06
		Trovafloxacin	0.004–0.12	0.03	0.06
		Ciprofloxacin	0.004–0.25	0.015	0.06
		Moxifloxacin	0.015–0.25	0.06	0.12
		Gatifloxacin	0.004–0.25	0.03	0.06
		Gemifloxacin	0.004–0.12	0.015	0.03

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TABLE 1—*Continued*

Strain	No. of isolates	Antibiotic	MIC (μg/ml)		
			Range	50% of strains	90% of strains
K. pneumoniae (ciprofloxacin resistant)	22	ABT-492	1–4	2	4
		Levofloxacin	4–32	16	16
		Trovafloxacin	4–64	16	32
		Ciprofloxacin	4–64	32	64
		Moxifloxacin	4–64	16	32
		Gatifloxacin	4–32	8	16
		Gemifloxacin	2–32	16	32
Klebsiella spp. (ciprofloxacin susceptible)	32	ABT-492	0.015–0.5	0.12	0.5
		Levofloxacin	0.03–2	0.12	2
		Trovafloxacin	0.015–4	0.12	1
		Ciprofloxacin	0.015–2	0.06	1
		Moxifloxacin	0.03–4	0.25	2
		Gatifloxacin	0.03–4	0.06	2
		Gemifloxacin	0.03–2	0.12	1
Enterobacter spp. (ciprofloxacin resistant)	4	ABT-492	32–128	NA	NA
		Levofloxacin	16–32	NA	NA
		Trovafloxacin	32–>128	NA	NA
		Ciprofloxacin	8–16	NA	NA
		Moxifloxacin	16–64	NA	NA
		Gatifloxacin	8–32	NA	NA
		Gemifloxacin	16–64	NA	NA
Enterobacter spp. (ciprofloxacin susceptible)	20	ABT-492	0.03–0.25	0.06	0.25
		Levofloxacin	0.03–0.5	0.06	0.12
		Trovafloxacin	0.015–0.25	0.06	0.12
		Ciprofloxacin	0.008–0.12	0.015	0.03
		Moxifloxacin	0.03–0.25	0.06	0.12
		Gatifloxacin	0.015–0.12	0.03	0.06
		Gemifloxacin	0.015–0.12	0.03	0.06
Providencia spp. (ciprofloxacin susceptible)	20	ABT-492	0.008–0.5	0.03	0.12
		Levofloxacin	0.03–0.5	0.12	0.25
		Trovafloxacin	0.015–1	0.12	0.5
		Ciprofloxacin	0.015–0.25	0.03	0.12
		Moxifloxacin	0.06–1	0.25	0.5
		Gatifloxacin	0.03–0.5	0.12	0.25
		Gemifloxacin	0.015–0.5	0.06	0.25
Proteus spp. (ciprofloxacin resistant)	1	ABT-492	2	NA	NA
		Levofloxacin	2	NA	NA
		Trovafloxacin	8	NA	NA
		Ciprofloxacin	2	NA	NA
		Moxifloxacin	8	NA	NA
		Gatifloxacin	4	NA	NA
		Gemifloxacin	8	NA	NA
Proteus spp. (ciprofloxacin susceptible)	40	ABT-492	0.03–0.12	0.06	0.12
		Levofloxacin	0.03–0.25	0.12	0.25
		Trovafloxacin	0.12–1	0.5	0.5
		Ciprofloxacin	0.03–0.25	0.06	0.12
		Moxifloxacin	0.12–1	0.5	1
		Gatifloxacin	0.06–0.5	0.25	0.5
		Gemifloxacin	0.12–0.25	0.25	0.25
Salmonella spp. (ciprofloxacin susceptible)	20	ABT-492	0.004–8	0.03	0.06
		Levofloxacin	0.015–0.5	0.03	0.06
		Trovafloxacin	0.015–0.5	0.03	0.06
		Ciprofloxacin	0.002–0.25	0.008	0.015
		Moxifloxacin	0.015–1	0.06	0.12
		Gatifloxacin	0.008–0.5	0.03	0.06
		Gemifloxacin	0.008–0.5	0.015	0.03

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TABLE 1—*Continued*

Strain	No. of isolates	Antibiotic	MIC (μg/ml)		
			Range	50% of strains	90% of strains
Serratia marcescens (ciprofloxacin susceptible)	10	ABT-492	0.25–2	0.5	2
		Levofloxacin	0.12–1	0.12	0.5
		Trovafloxacin	0.25–2	0.5	1
		Ciprofloxacin	0.03–0.25	0.06	0.25
		Moxifloxacin	0.25–2	0.5	1
		Gatifloxacin	0.12–2	0.5	0.5
		Gemifloxacin	0.12–2	0.5	1
Citrobacter freundii (ciprofloxacin susceptible)	20	ABT-492	0.015–2	0.06	1
		Levofloxacin	0.015–0.5	0.03	0.25
		Trovafloxacin	0.015–0.5	0.03	0.5
		Ciprofloxacin	0.008–0.12	0.015	0.12
		Moxifloxacin	0.03–1	0.12	1
		Gatifloxacin	0.015–0.5	0.06	0.5
		Gemifloxacin	0.015–0.5	0.03	0.25
P. aeruginosa (ciprofloxacin resistant)	21	ABT-492	1–>128	32	128
		Levofloxacin	8–>128	64	>128
		Trovafloxacin	4–>128	>128	>128
		Ciprofloxacin	2–128	32	128
		Moxifloxacin	16–>128	128	>128
		Gatifloxacin	8–>128	64	128
		Gemifloxacin	4–>128	128	>128
P. aeruginosa (ciprofloxacin susceptible)	19	ABT-492	0.06–2	0.25	0.5
		Levofloxacin	0.25–2	0.5	1
		Trovafloxacin	0.12–4	0.5	1
		Ciprofloxacin	0.06–2	0.12	0.5
		Moxifloxacin	0.25–16	1	2
		Gatifloxacin	0.12–8	0.5	1
		Gemifloxacin	0.12–4	0.25	1
Stenotrophomonas maltophilia (ciprofloxacin susceptible)	19	ABT-492	0.12–16	1	2
		Levofloxacin	0.5–16	2	4
		Trovafloxacin	0.5–16	1	2
		Ciprofloxacin	1–32	4	8
		Moxifloxacin	0.12–8	1	2
		Gatifloxacin	0.25–16	2	4
		Gemifloxacin	0.25–16	2	4
Burkholderia cepacia (ciprofloxacin resistant)	12	ABT-492	0.25–16	4	16
		Levofloxacin	2–>128	16	128
		Trovafloxacin	1–>128	16	64
		Ciprofloxacin	2–>128	16	>128
		Moxifloxacin	1–128	16	128
		Gatifloxacin	2–128	16	128
		Gemifloxacin	2–32	16	32
Burkholderia cepacia (ciprofloxacin susceptible)	1	ABT-492	0.25	NA	NA
		Levofloxacin	1	NA	NA
		Trovafloxacin	1	NA	NA
		Ciprofloxacin	1	NA	NA
		Moxifloxacin	1	NA	NA
		Gatifloxacin	1	NA	NA
		Gemifloxacin	4	NA	NA
Acinetobacter spp. (ciprofloxacin resistant)	14	ABT-492	1–32	2	16
		Levofloxacin	4–128	16	64
		Trovafloxacin	1–>128	8	>128
		Ciprofloxacin	32–>128	128	>128
		Moxifloxacin	4–128	16	64
		Gatifloxacin	4–128	16	128
		Gemifloxacin	2–128	16	64

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TABLE 1—*Continued*

Strain	No. of isolates	Antibiotic	MIC (μg/ml)		
			Range	50% of strains	90% of strains
Acinetobacter spp. (ciprofloxacin susceptible)	14	ABT-492	≤0.001–0.5	0.12	0.25
		Levofloxacin	0.015–1	0.25	0.5
		Trovafloxacin	0.004–0.12	0.03	0.06
		Ciprofloxacin	0.015–1	0.25	1
		Moxifloxacin	0.015–0.25	0.06	0.12
		Gatifloxacin	0.008–0.25	0.06	0.25
		Gemifloxacin	0.004–0.25	0.06	0.12

[a] NA, not applicable. MIC_{50}s and MIC_{90}s were not calculated when the n number of isolates was less than 9.

lone-susceptible *S. pneumoniae*, *Streptococcus pyogenes*, *S. aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Enterococcus faecium*. For quinolone-resistant *S. pneumoniae*, *S. aureus* (including methicillin-resistant *S. aureus*), and *S. epidermidis*, ABT-492 MIC_{90}s were 0.5 to 1 μg/ml. None of the antibiotics had significant activity against quinolone-resistant *E. faecalis* and *E. faecium*.

As expected, ABT-492 activity against *S. pneumoniae* was unaffected by altered penicillin-binding proteins since the MIC_{50}s and MIC_{90}s remained the same or were similar among penicillin-susceptible (MIC_{50} and MIC_{90} = 0.015 and 0.25 μg/ml, respectively), -intermediate (0.008 and 0.25 μg/ml), and -resistant (0.015 and 0.25 μg/ml) isolates. The ABT-492 MIC_{90} reflects the fact that 28, 21, and 36% of penicillin-susceptible, -intermediate, and -resistant isolates were quinolone resistant, respectively. Comparator quinolone activity was also unaffected by penicillin susceptibility.

Oxacillin susceptibility did not affect ABT-492 activity (MIC_{90} = 0.06 μg/ml) among oxacillin-susceptible *S. aureus* isolates. Sixteen and 92% of the oxacillin-susceptible and -resistant strains, respectively, were quinolone resistant. The ABT-492 MIC_{90} was 1 μg/ml for oxacillin- and quinolone-resistant *S. aureus*.

Likewise, ABT-492 activity against *E. faecalis* and *E. faecium* was unaffected by vancomycin susceptibility. The ABT-492 MIC_{90} was 8 μg/ml against vancomycin-susceptible *E. faecalis* and *E. faecium* and vancomycin-resistant *E. faecium*, and the MIC range was 0.12 to 0.5 μg/ml for vancomycin-resistant *E. faecalis* (data not shown).

ABT-492 (MIC_{90}, ≤0.004 μg/ml) was the most potent quinolone against quinolone-susceptible *H. influenzae* and *Moraxella catarrhalis*.

Against members of the family *Enterobacteriaceae*, ABT-492 (MIC_{90}s = 0.06 to 0.5 μg/ml) and ciprofloxacin (MIC_{90}s = 0.06 to 1 μg/ml) had equivalent activities for quinolone-susceptible *E. coli*, *Klebsiella* spp., *Providencia* spp., and *Proteus* spp. Ciprofloxacin (MIC_{90}s = 0.015 to 0.25 μg/ml) had improved activity, compared to that of ABT-492 (MIC_{90}s = 0.06 to 0.2 μg/ml), against quinolone-susceptible *Enterobacter* spp., *Salmonella* spp., *Serratia marcescens*, and *Citrobacter freundii*. ABT-492 (MIC_{90}s = 4 to 8 μg/ml) was the most potent quinolone against quinolone-resistant *E. coli* and *K. pneumoniae*. ABT-492 (MICs = 32 to 128 μg/ml) had no activity against four isolates of quinolone-resistant *Enterobacter* spp.

ABT-492 (MIC_{90s} = 0.25 to 2 μg/ml) and the other quinolones had comparable activity against quinolone-susceptible *P. aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter* spp., and the single isolate of *Burkholderia cepacia*. None were active against quinolone-resistant *P. aeruginosa*, *Acinetobacter* spp., or *B. cepacia*.

For quinolone-susceptible strains, ABT-492, ciprofloxacin, and moxifloxacin at four and eight times the MICs were bactericidal (≥3-$\log_{10}$ decrease [99.9% killing] in the number of CFU per milliliter compared to that of the starting inoculum) for all three drugs at both concentrations within 4 h for *S. aureus*, *E. coli*, and *P. aeruginosa* and within 10 h for *S. pneumoniae*.

ABT-492 and moxifloxacin were bactericidal at both four and eight times the MICs of both drugs for quinolone-resistant strains of *E. coli* (GyrA, Ser83-Leu and Asp87-Asn; ParC, Ser80-Ile) (ABT-492 only; moxifloxacin MIC, ≥32 μg/ml) within 6 h, *S. aureus* (GyrA, Ser84-Leu; GrlA, Ser80-Phe) within 10 h, and *S. pneumoniae* (GyrA, Ser81-Phe; ParC, Ser79-Phe) by 24 h. Ciprofloxacin was not evaluated (MIC, ≥64 μg/ml).

ABT-492 is a broad-spectrum quinolone displaying improved in vitro and bactericidal activities against a variety of quinolone-susceptible and -resistant gram-positive and gram-negative organisms, which suggests that it may be useful for treating many different types of infections.

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