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In Vitro Activity of Bay Y3118 against Anaerobic Bacteria

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The antimicrobial activity of a new quinolone, Bay Y3118, was determined against 326 strains of anaerobic bacteria and compared with the activities of ampicillin-sulbactam, cefotetan, clindamycin, imipenem, metronidazole, and sparfloxacin. The National Committee for Clinical Laboratory Standards-approved Wadsworth agar dilution technique with *Brucella*-laked blood agar was used throughout the study. Breakpoints used to determine the percent susceptible were 2 μg/ml for Bay Y3118 and sparfloxacin, 4 μg/ml for clindamycin, 8 μg/ml for imipenem, 16 μg/ml for metronidazole and ampicillin-sulbactam, and 32 μg/ml for cefotetan. Species tested included *Bacteroides fragilis* (57 strains), other *B. fragilis* group species (79 strains), *Bacteroides gracilis* (10 strains), other *Bacteroides* spp. (9 strains), *Prevotella* spp. (30 strains), *Porphyromonas* spp. (9 strains), *Fusobacterium* spp. (36 strains), *Bilophila wadsworthia* (14 strains), *Clostridium* spp. (36 strains), *Peptostreptococcus* spp. (20 strains), and gram-positive non-spore-forming rods (26 strains). Bay Y3118 inhibited all but 1 of 326 anaerobic bacteria tested at the breakpoint level or lower.

Most of the quinolone agents introduced over the past several years, including ciprofloxacin, lomefloxacin, norfloxacin, pefloxacin, enoxacin, cinoxacin, and ofloxacin, have had only limited activity against anaerobes. Activity against the *Bacteroides fragilis* group organisms has been poor, in general (2, 4, 5, 8, 9, 15, 18). Variable activity against *Prevotella* species, such as the *Prevotella melaninogenica* and *Prevotella oralis* group, and against *Bacteroides ureolyticus* has been reported (8). The newer quinolones, e.g., sparfloxacin and WIN 57273, have increased activity against *B. fragilis* (6, 17, 20) (78 and 100% susceptible, respectively, in our studies). WIN 57273 also inhibited all other species of the *B. fragilis* group tested. The purpose of this study was to evaluate the in vitro activity of a new quinolone, Bay Y3118, against a wide variety of clinical isolates of anaerobic organisms. Bay Y3118 is a halogenated quinolone, characterized by substituents at the −7 and −8 positions (21), that has potent antibacterial activity against a broad spectrum of bacteria (1, 3, 10, 13, 16).

All bacteria were randomly selected recent clinical isolates from the Veterans Affairs Wadsworth Medical Center, Los Angeles, Calif. Bacteria were identified according to established procedures (7, 14). MICs were determined by an agar dilution technique described previously (14) with an inoculum of 10^5 CFU and *Brucella* base-laked blood agar. Plates were incubated in GasPak jars or in an anaerobic chamber (Anaerobe Systems, San Jose, Calif.) for 48 h at 37°C. MICs were defined as the lowest concentration of antimicrobial agent permitting no growth, one discrete colony, a barely visible haze, or any distinct change from the growth control (11). Reference strains of *B. fragilis* (ATCC 25285) and *Bacteroides thetaiotaomicron* (ATCC 29741) were used as controls in each test. β-Lactamase production was determined by the use of nitrocefin disks (Cefinase, BBL) according to manufacturer's directions. Antimicrobial agents were obtained as powders from various companies as follows: Bay Y3118 (Miles Pharmaceuticals, West Haven, Conn.), ampicillin and sulbactam (Pfizer Pharmaceuticals, New York, N.Y.); cefotetan (ICI Pharmaceuticals, Wilmington, Del.), sparfloxacin (Parke-Davis, Warner Lambert Co., Ann Arbor, Mich.), imipenem (Merck Sharp & Dohme, Rahway, N.J.), clindamycin (The Upjohn Company, Kalamazoo, Mich.), and metronidazole (Sigma, St. Louis, Mo.). Ampicillin and sulbactam were used in a 2:1 ratio.

Breakpoints used to determine percents susceptible are listed in footnote *a* to Table 1. When available, National Committee for Clinical Laboratory Standards-approved breakpoints were used. Other breakpoints are those suggested by the manufacturer. Results of these studies are listed in Table 1. Percents susceptible are reported over a three-twofold-dilution range bracketing the breakpoint. If enough strains of one species were tested to give meaningful results, those data are listed separately. The particular species tested for each genus are listed in footnotes to Table 1. In a few cases, even if fewer than 10 strains were tested, the results were computed separately if they were very different from the results for the rest of the group.

Bay Y3118 inhibited all strains of *B. fragilis* at ≤0.5 μg/ml and all but one strain of other *B. fragilis* group species at 0.5 μg/ml (the MIC for one strain of *Bacteroides ovatus* was 2 μg/ml). The MIC for 90% of strains tested (MIC_{90}) for the *B. fragilis* strains was ≤0.125 μg/ml. Ampicillin-sulbactam, imipenem, and metronidazole also inhibited all strains of *B. fragilis* at their respective breakpoints (MIC_{90}s were 4, 0.25, and 2 μg/ml, respectively). One strain of *B. ovatus* was resistant to ampicillin-sulbactam (MIC, 32 μg/ml); imipenem and metronidazole inhibited all strains of other *B. fragilis* group species. Clindamycin inhibited 90 and 80%, respectively, of *B. fragilis* and other *B. fragilis* group species at its breakpoint of 4 μg/ml. Sparfloxacin inhibited 93% both of *B. fragilis* strains and of other *B. fragilis* group species at 2 μg/ml (MIC_{90}, 2 μg/ml). Cefotetan inhibited 92% of *B. fragilis* strains at 32 μg/ml, but only 60% of other *B. fragilis* group species, in agreement with earlier reports from our laboratory (19).

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TABLE 1. Activity of antimicrobial agents against various organisms

Organism (no. of strains) and antimicrobial agent	MIC range	MIC_{50}	MIC_{90}	%s Susceptible[a]
Bacteroides fragilis (57)				
Ampicillin-sulbactam[b]	0.125–16	1	4	97, 100, 100
Bay Y3118	0.062–0.5	0.062	0.125	100, 100, 100
Cefotetan	1–128	4	32	86, 92, 98
Clindamycin	0.062–>32	1	2	90, 90, 92
Imipenem	0.062–1	0.125	0.25	100, 100, 100
Metronidazole	0.25–4	1	2	100, 100, 100
Sparfloxacin	0.25–16	1	2	75, 93, 97
Other *Bacteroides fragilis* group species[c] (79)				
Ampicillin-sulbactam	0.125–32	2	8	93, 98, 100
Bay Y3118	0.062–2	0.125	0.25	99, 100, 100
Cefotetan	1–>256	32	64	38, 60, 90
Clindamycin	0.062–>32	2	64	63, 80, 85
Imipenem	0.062–4	0.25	1	100, 100, 100
Metronidazole	0.125–4	1	2	100, 100, 100
Sparfloxacin	0.25–8	2	2	48, 93, 99
Bacteroides gracilis (10)				
Ampicillin-sulbactam	0.125–8	2	8	100, 100, 100
Bay Y3118	0.062–0.25	0.062	0.062	100, 100, 100
Cefotetan	1–16	2	8	100, 100, 100
Clindamycin	0.25–8	2	8	60, 80, 100
Imipenem	0.25–8	1	2	90, 100, 100
Metronidazole	0.125–128	1	128	60, 70, 70
Sparfloxacin	0.25–8	0.25	0.5	90, 90, 90
Other *Bacteroides* species[d] (9)				
Ampicillin-sulbactam	0.125–8	—[e]	—	100, 100, 100
Bay Y3118	0.062–0.5	—	—	100, 100, 100
Cefotetan	1–128	—	—	89, 89, 89
Clindamycin	0.062–>32	—	—	78, 89, 89
Imipenem	0.062–0.5	—	—	100, 100, 100
Metronidazole	0.125–4	—	—	100, 100, 100
Sparfloxacin	0.25–8	—	—	56, 67, 89
Porphyromonas species[f] (9)				
Ampicillin-sulbactam	0.125–1	—	—	100, 100, 100
Bay Y3118	0.062–0.125	—	—	100, 100, 100
Cefotetan	1–4	—	—	100, 100, 100
Clindamycin	0.062–>32	—	—	90, 90, 90
Imipenem	0.062–0.062	—	—	100, 100, 100
Metronidazole	0.125–0.25	—	—	100, 100, 100
Sparfloxacin	0.25–2	—	—	80, 100, 100
Prevotella species[g] (30)				
Ampicillin-sulbactam	0.125–4	0.25	2	100, 100, 100
Bay Y3118	0.062–1	0.125	0.5	100, 100, 100
Cefotetan	1–64	2	8	94, 97, 100
Clindamycin	0.062–0.062	0.062	0.062	100, 100, 100
Imipenem	0.062–0.5	0.062	0.125	100, 100, 100
Metronidazole	0.125–4	1	2	100, 100, 100
Sparfloxacin	0.5–16	2	4	24, 70, 91
Bilophila wadsworthia (14)				
Ampicillin-sulbactam	2–8	4	4	100, 100, 100
Bay Y3118	0.062–0.125	0.062	0.125	100, 100, 100
Cefotetan	1–16	4	4	100, 100, 100
Clindamycin	0.125–0.25	0.25	0.25	100, 100, 100
Imipenem	0.25–0.25	0.25	0.25	100, 100, 100
Metronidazole	0.125–0.125	0.125	0.125	100, 100, 100
Sparfloxacin	0.25–1	0.5	1	100, 100, 100
Fusobacterium nucleatum (15)				
Ampicillin-sulbactam	0.125–0.5	0.125	0.125	100, 100, 100
Bay Y3118	0.062–4	0.062	0.125	94, 94, 100
Cefotetan	1–16	1	2	100, 100, 100
Clindamycin	0.062–0.125	0.062	0.125	100, 100, 100

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TABLE 1—*Continued*

Organism (no. of strains) and antimicrobial agent	MIC range	MIC_{50}	MIC_{90}	%s Susceptible[a]
Imipenem	0.062–0.125	0.062	0.125	100, 100, 100
Metronidazole	0.125–0.5	0.125	0.25	100, 100, 100
Sparfloxacin	0.5–64	1	2	88, 94, 94
Fusobacterium mortiferum/varium group (12)				
Ampicillin-sulbactam	1–8	2	8	100, 100, 100
Bay Y3118	0.062–1	0.5	1	100, 100, 100
Cefotetan	1–4	2	4	100, 100, 100
Clindamycin	0.062–8	2	8	75, 75, 100
Imipenem	0.125–2	0.5	2	100, 100, 100
Metronidazole	0.125–1	0.5	0.5	100, 100, 100
Sparfloxacin	1–16	8	16	17, 33, 33
Other *Fusobacterium* species[b] (9)				
Ampicillin-sulbactam	0.125–4	—	—	100, 100, 100
Bay Y3118	0.125–2	—	—	89, 100, 100
Cefotetan	1–32	—	—	89, 100, 100
Clindamycin	0.062–4	—	—	89, 100, 100
Imipenem	0.062–1	—	—	100, 100, 100
Metronidazole	0.125–1	—	—	100, 100, 100
Sparfloxacin	1–16	—	—	33, 56, 78
Clostridium difficile (10)				
Ampicillin-sulbactam	1–8	4	8	100, 100, 100
Bay Y3118	0.25–0.5	0.5	0.5	100, 100, 100
Cefotetan	8–>256	16	32	80, 90, 90
Clindamycin	1–>32	64	64	10, 20, 40
Imipenem	4–8	4	8	50, 100, 100
Metronidazole	0.125–0.5	0.25	0.5	100, 100, 100
Sparfloxacin	2–8	8	8	0, 10, 40
Clostridium perfringens (10)				
Ampicillin-sulbactam	0.125–0.25	0.125	0.125	100, 100, 100
Bay Y3118	0.125–0.25	0.125	0.125	100, 100, 100
Cefotetan	1–2	1	1	100, 100, 100
Clindamycin	0.062–4	1	4	70, 100, 100
Imipenem	0.062–0.5	0.125	0.25	100, 100, 100
Metronidazole	0.5–2	0.5	1	100, 100, 100
Sparfloxacin	0.25–2	0.5	0.5	90, 100, 100
Clostridium ramosum (10)				
Ampicillin-sulbactam	0.125–0.5	0.25	0.5	100, 100, 100
Bay Y3118	0.25–0.5	0.5	0.5	100, 100, 100
Cefotetan	1–32	2	32	80, 100, 100
Clindamycin	2–>32	4	64	20, 60, 70
Imipenem	0.25–0.5	0.25	0.5	100, 100, 100
Metronidazole	1–2	1	1	100, 100, 100
Sparfloxacin	1–4	2	2	20, 90, 100
Other *Clostridium* species[i] (6)				
Ampicillin-sulbactam	0.125–2	—	—	100, 100, 100
Bay Y3118	0.125–2	—	—	86, 100, 100
Cefotetan	1–>256	—	—	71, 71, 71
Clindamycin	0.062–8	—	—	86, 86, 100
Imipenem	0.062–4	—	—	100, 100, 100
Metronidazole	0.125–4	—	—	100, 100, 100
Sparfloxacin	0.25–32	—	—	43, 57, 57
Peptostreptococcus species[j] (20)				
Ampicillin-sulbactam	0.125–8	0.125	0.5	100, 100, 100
Bay Y3118	0.062–0.5	0.062	0.125	100, 100, 100
Cefotetan	1–8	1	4	100, 100, 100
Clindamycin	0.062–1	0.125	1	100, 100, 100
Imipenem	0.062–0.5	0.062	0.062	100, 100, 100
Metronidazole	0.125–2	0.5	2	100, 100, 100
Sparfloxacin	0.25–8	0.25	1	90, 90, 90

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TABLE 1—*Continued*

Organism (no. of strains) and antimicrobial agent	MIC range	MIC_{50}	MIC_{90}	%s Susceptible[a]
Gram-positive rods (non-spore-forming)[k] (26)				
Ampicillin-sulbactam	0.125–4	0.25	2	100, 100, 100
Bay Y3118	0.062–0.5	0.062	0.5	100, 100, 100
Cefotetan	1–>256	1	32	75, 96, 96
Clindamycin	0.062–2	0.125	1	100, 100, 100
Imipenem	0.062–0.5	0.062	0.5	100, 100, 100
Metronidazole	0.125–>128	4	>256	54, 61, 68
Sparfloxacin	0.125–8	0.5	8	68, 79, 79
Total (326)				
Ampicillin-sulbactam	0.125–32	1	4	98, 99, 100
Bay Y3118	0.062–4	0.125	0.5	99, 99, 100
Cefotetan	1–>256	4	64	78, 87, 96
Clindamycin	0.062–>32	0.25	8	80, 88, 92
Imipenem	0.062–8	0.125	1	98, 100, 100
Metronidazole	0.125–>128	0.5	2	95, 96, 96
Sparfloxacin	0.125–64	1	8	58, 83, 89

[a] Percents susceptible are reported at 1 dilution below the breakpoint, at the breakpoint, and at 1 dilution above the breakpoint. Breakpoints used to determine the percents susceptible were 2 μg/ml for Bay Y3118 and sparfloxacin, 4 μg/ml for clindamycin, 8 μg/ml for imipenem, 16 μg/ml for metronidazole and ampicillin-sulbactam, and 32 μg/ml for cefotetan. Breakpoints are as approved by the National Committee for Clinical Laboratory Standards, except for the 2-μg/ml breakpoint for Bay Y3118 and sparfloxacin. These were included for purposes of comparison with other quinolones. No breakpoint for these compounds has been approved as yet by the National Committee for Clinical Laboratory Standards.

[b] Ampicillin and sulbactam were prepared in a 2:1 ratio.

[c] Includes (numbers of strains are in parentheses) *Bacteroides caccae* (3), *B. distasonis* (13), *Bacteroides eggerthii* (2), *Bacteroides merdae* (1), *B. ovatus* (7), *Bacteroides stercoris* (3), *B. thetaiotaomicron* (29), *Bacteroides uniformis* (8), and *Bacteroides vulgatus* (13).

[d] Includes (numbers of strains are in parentheses) *B. ureolyticus* (2), *Bacteroides splanchnicus* (1), *Bacteroides capillosus* (1), and other *Bacteroides* species (5).

[e] No MIC_{50}s or MIC_{90}s are reported if the number of strains tested is less than 10.

[f] Includes (numbers of strains are in parentheses) *Porphyromonas asaccharolytica* (3), *Porphyromonas endodontalis* (4), and *Porphyromonas gingivalis* (2).

[g] Includes (numbers of strains are in parentheses) *Prevotella bivia* (5), *Prevotella corporis* (1), *Prevotella denticola* (2), *Prevotella disiens* (2), *Prevotella intermedia* (7), *Prevotella loescheii* (4), *P. melaninogenica* (4), *Prevotella oris* (1), and *Prevotella zoogleoformans* (1), and other *Prevotella* species (3).

[h] Includes (numbers of strains are in parentheses) *Fusobacterium gonidiaformans* (2), *Fusobacterium naviforme* (1), *Fusobacterium necrogenes* (1), *Fusobacterium necrophorum* (2), and other *Fusobacterium* species (3).

[i] Includes (numbers of strains are in parentheses) *Clostridium clostridiiforme* (1), *Clostridium innocuum* (1), *Clostridium sordellii* (1), *Clostridium sporosphaeroides* (1), *Clostridium subterminale* (1), and other *Clostridium* species (1).

[j] Includes (numbers of strains in parentheses) *Peptostreptococcus anaerobius* (1), *Peptostreptococcus asaccharolyticus* (4), *Peptostreptococcus magnus* (3), *Peptostreptococcus micros* (4), *Peptostreptococcus prevotii* (2), *Peptostreptococcus productus* (1), *Peptostreptococcus tetradius* (2), and other *Peptostreptococcus* species (3).

[k] Includes (numbers of strains are in parentheses) *Actinomyces israelii* (2), *Actinomyces odontolyticus* (3), *Actinomyces* species (2), *Eubacterium aerogenes* (1), *Eubacterium lentum* (5), *Eubacterium limosum* (2), other *Eubacterium* species (2), *Lactobacillus catenaformis* (1), *Lactobacillus minutus* (1), other *Lactobacillus* species (2), *Propionibacterium acnes* (3), other *Propionibacterium* species (1), and unidentified gram-positive rods (1).

All strains of *Bacteroides gracilis*, other *Bacteroides* species, *Bilophila wadsworthia*, *Porphyromonas* spp., *Prevotella* spp., *Clostridium* spp., *Peptostreptococcus* spp., and non-spore-forming gram-positive rods were inhibited by Bay Y3118 at breakpoint. One strain of *Fusobacterium nucleatum* was resistant (MIC, 4 μg/ml; the MIC for sparfloxacin was 64 μg/ml). Ampicillin-sulbactam and imipenem inhibited all strains of *B. gracilis*, other *Bacteroides* species, *Bilophila wadsworthia*, *Fusobacterium* spp., *Porphyromonas* spp., *Prevotella* spp., *Peptostreptococcus* spp., *Clostridium* spp., and non-spore-forming gram-positive rods at breakpoint. In accordance with other data, 39% of non-spore-forming gram-positive rods were resistant (19). Metronidazole inhibited all strains of gram-negative anaerobes except for three strains of *B. gracilis* (strains belonging to this species are currently undergoing taxonomic revision and will probably be split into several groups.) Clindamycin, sparfloxacin, and cefotetan gave results similar to those reported in other publications (19, 20). Some of the organisms used in this study were tested for β-lactamase activity with nitrocefin disks, and the results are listed in Table 2; most of the *B. fragilis* organisms and more than half of the *Prevotella* strains were nitrocefin positive. Of the *B. fragilis* group, the lowest percentage of nitrocefin-positive strains were seen in the species *Bacteroides distasonis*.

Many of the newly introduced quinolones have good-to-excellent activity against anaerobes (20). Several reports from the 1992 Interscience Conference on Antimicrobial Agents and Chemotherapy (1, 3, 10, 13, 16) as well as a recent publication (12) have also reported better activity than that of the currently available quinolones (e.g., ciprofloxacin and sparfloxacin) against a range of aerobic and anaerobic bacteria. There have not yet been enough clinical trials to determine whether emerging resistance will be a problem. Additional clinical trials are needed to ascertain how useful these agents will be for therapy of mixed aerobic-anaerobic infections.

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TABLE 2. β-Lactamase production in anaerobic bacteria tested (as determined by hydrolysis of nitrocefin)

Organism(s)	% Positive (no. positive/no. tested) or no. tested[a]
Nitrocefin positive	
B. fragilis	90 (27/30)
Other *B. fragilis* group spp.	84 (48/57)
B. caccae	100 (1/1)
B. distasonis	36 (4/11)
B. ovatus	100 (4/4)
B. stercoris	67 (2/3)
B. thetaiotaomicron	100 (21/21)
B. uniformis	100 (7/7)
B. vulgatus	100 (9/9)
B. splanchnicus	100 (1/1)
Other *Bacteroides* spp.	100 (1/1)
B. wadsworthia	100 (1/1)
F. necrophorum	33 (1/3)
Prevotella spp.	57 (8/14)
Nitrocefin negative[b]	
B. gracilis	6
B. eggerthii	1
B. ureolyticus	2
Porphyromonas spp.	3
Fusobacterium spp.	25
Clostridium spp.	11
Peptostreptococcus spp.	6
Non-spore-forming gram-positive rods	7

[a] For nitrocefin-negative organisms, only the number tested is given.
[b] All strains of these species tested were nitrocefin negative, except for one strain of *F. necrophorum*, which is listed under nitrocefin-positive organisms.

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