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In Vitro Activity of DU-6859a against Anaerobic Bacteria

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The activity of a new quinolone agent, DU-6859a, against 330 strains of anaerobic bacteria was determined by using the National Committee for Clinical Laboratory Standards-approved Wadsworth brucella laked blood agar method; the activity of DU-6859a was compared with those of amoxicillin-clavulanate (2:1), chloramphenicol, ciprofloxacin, clindamycin, fleroxacin, imipenem, lomefloxacin, metronidazole, sparfloxacin, and temafloxacin. DU-6859a and chloramphenicol inhibited all of the isolates at concentrations of 1 and 16 μg/ml, respectively; amoxicillin-clavulanate, imipenem, and metronidazole inhibited ≥94% of the isolates at their respective breakpoints (8, 8, and 16 μg/ml). MICs of DU-6859a at which 90% of the strains were susceptible were 1 to 5 twofold dilutions lower than those of the other quinolones for every group of organisms. MICs of DU-6859a at which 90% of the strains were susceptible (total numbers of strains tested are in parentheses) were ≤0.25 μg/ml for *Bacteroides fragilis* (57), other *B. fragilis* group species (84), *Bilophila wadsworthia* (15), *Clostridium* species (27) (including *C. difficile*, *C. perfringens*, and *C. ramosum*), *Fusobacterium nucleatum* (16), *Fusobacterium mortiferum-F. varium* group species (10), *Peptostreptococcus* species (20), non-spore-forming gram-positive rods (20), and *Prevotella* species (25).

The broad antibacterial spectra and favorable pharmacokinetics of fluoroquinolones have resulted in their becoming important antibacterial agents. However, most of them (e.g., ciprofloxacin, lomefloxacin, norfloxacin, and ofloxacin) have only mediocre activity against anaerobes and very poor activity against the *Bacteroides fragilis* group. Activity against anaerobes in general, and the *B. fragilis* group in particular, has been markedly improved in the case of the new quinolones undergoing evaluation. Several such agents were recently tested in our laboratory and were found to be very active against *B. fragilis* (WIN 57273, BayY 3118, and clinafloxacin [CI-960] inhibited all strains tested at concentrations of ≤2 μg/ml) (6, 12–14). DU-6859a is a new orally administered N_1-fluorocyclopropylquinolone with a *cis*-2-fluorocyclopropanecarboxylic acid which is responsible for its reduced side effects and good pharmacokinetic profiles (8, 10). A number of reports presented at the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy indicated that this compound was more active than related compounds against a wide range of organisms. This report describes the activity of DU-6859a against a wide variety of recently isolated anaerobic organisms.

Antimicrobial agents were obtained as powders from the indicated suppliers: DU-6859a (Daiichi Pharmaceutical Co., Tokyo, Japan); sparfloxacin (Warner-Lambert Co., Ann Arbor, Mich.); lomefloxacin (G. D. Searle and Company, Skokie, Ill.); fleroxacin (Hoffmann-La Roche, Nutley, N.J.); clindamycin (Upjohn, Kalamazoo, Mich.); imipenem (Merck, Sharp and Dohme, Rahway, N.J.); and amoxicillin-clavulanic acid (SmithKline Beecham, Philadelphia, Pa.), ciprofloxacin, chloramphenicol, and metronidazole (Sigma, St. Louis, Mo.).

All bacteria were randomly selected recent clinical isolates from the Veterans Administration Wadsworth Medical Center, Los Angeles. Bacteria were identified according to established procedures (2, 9). MICs were determined by an agar dilution technique described previously (7, 9) by using an inoculum of 10^5 CFU and brucella 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 concentrations of antimicrobial agents resulting in a marked change in the appearance of growth in comparison with the control plate (7). Reference strains of *B. fragilis* (ATCC 25285) and *Bacteroides thetaiotaomicron* (ATCC 29741) were used as controls in each test. *Bacteroides gracilis* strains were tested on brucella laked blood agar (BLBA) with fumarate and formate (0.3% each) added; *Bilophila wadsworthia* was tested on BLBA with pyruvate (1%). β-Lactamase production was determined by the use of nitrocefin disks (Cefinase; BBL, Cockeysville, Md.) according to the manufacturer's directions.

The in vitro activities of the agents tested are listed in Table 1. No breakpoints have yet been approved for DU-6859a, and there are no National Committee for Clinical Laboratory Standards (NCCLS)-approved breakpoints for the other quinolone agents for use with anaerobes (the NCCLS-approved breakpoint for ciprofloxacin for use with aerobes is 1 μg/ml). NCCLS-approved breakpoints have been established for clindamycin (4 μg/ml), imipenem (8 μg/ml), amoxicillin-clavulanic acid (8 μg/ml), metronidazole (16 μg/ml), and chloramphenicol (16 μg/ml) for use with anaerobes.

Ninety-four percent of the *B. fragilis* strains produced β-lactamase, and 84% of the other *B. fragilis* group organisms were positive for β-lactamase production. Other organisms which showed demonstrable β-lactamase production were *Bilophila wadsworthia* (87% positive) and *Prevotella* species (56% positive). None of the *Fusobacterium* strains tested were Cefinase positive. Among the gram-positive organisms, only one strain of *Peptostreptococcus tetradius* and one strain of *Propionibacterium acnes* were positive.

DU-6859a had excellent activity against anaerobes. All strains tested were inhibited at 1 μg/ml, including two imi-

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TABLE 1. Activities of antimicrobial agents against various organisms

Microorganism (no. of isolates)	Antimicrobial agent	MIC (μg/ml)[a]		
		Range	50%	90%
B. fragilis (57)	Amoxicillin-clavulanic acid	0.5–64	1	4
	Chloramphenicol	2–16	8	8
	Ciprofloxacin	0.5–>64	4	32
	Clindamycin	0.125–>32	1	>32
	DU-6859	0.062–0.5	0.062	0.25
	Fleroxacin	4–32	8	16
	Imipenem	0.062–>64	0.125	0.5
	Lomefloxacin	2–64	8	16
	Metronidazole	0.25–2	0.5	1
	Sparfloxacin	0.25–16	2	4
	Temafloxacin	0.5–8	1	2
Other *B. fragilis* group species (84)[b]	Amoxicillin-clavulanic acid	0.5–16	2	8
	Chloramphenicol	2–16	8	8
	Ciprofloxacin	0.5–>64	16	64
	Clindamycin	0.125–>32	4	>32
	DU-6859	0.062–1	0.25	0.5
	Fleroxacin	2–>64	16	64
	Imipenem	0.062–4	0.25	1
	Lomefloxacin	2–>64	16	32
	Metronidazole	0.125–8	1	2
	Sparfloxacin	0.25–16	2	8
	Temafloxacin	0.5–8	2	4
B. gracilis (10)[c]	Amoxicillin-clavulanic acid	0.125–16	4	8
	Chloramphenicol	0.5–4	2	2
	Ciprofloxacin	0.25–1	0.5	0.5
	Clindamycin	0.25–8	4	8
	DU-6859	0.25–0.25	0.25	0.25
	Fleroxacin	0.25–2	0.5	1
	Imipenem	0.125–2	1	2
	Lomefloxacin	0.25–2	1	1
	Metronidazole	0.5–64	0.5	64
	Sparfloxacin	0.25–2	0.25	0.5
	Temafloxacin	0.25–2	0.25	0.5
Other *Bacteroides* species (12)[d]	Amoxicillin-clavulanic acid	0.125–1	0.25	0.5
	Chloramphenicol	0.5–4	2	4
	Ciprofloxacin	0.25–32	2	8
	Clindamycin	0.125–0.5	0.125	0.5
	DU-6859	0.062–1	0.062	0.25
	Fleroxacin	0.25–16	8	16
	Imipenem	0.062–0.25	0.062	0.25
	Lomefloxacin	0.5–32	8	16
	Metronidazole	0.125–16	0.5	4
	Sparfloxacin	0.25–4	2	4
	Temafloxacin	0.25–8	1	4
Porphyromonas species (9)[e]	Amoxicillin-clavulanic acid	0.125–0.125	0.125	
	Chloramphenicol	2–8	4	
	Ciprofloxacin	0.5–4	1	
	Clindamycin	0.125–>32	0.125	
	DU-6859	0.062–0.25	0.062	
	Fleroxacin	1–8	4	
	Imipenem	0.062–0.062	0.062	
	Lomefloxacin	1–8	4	
	Metronidazole	0.125–0.5	0.125	
	Sparfloxacin	0.25–2	1	
	Temafloxacin	0.25–8	1	
Prevotella species (25)[f]	Amoxicillin-clavulanic acid	0.125–4	0.25	0.5
	Chloramphenicol	1–4	2	4
	Ciprofloxacin	1–16	2	4
	Clindamycin	0.125–0.125	0.125	0.125
	DU-6859	0.062–0.25	0.062	0.25
	Fleroxacin	2–16	4	16
	Imipenem	0.062–0.062	0.062	0.062

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TABLE 1—*Continued*

Microorganism (no. of isolates)	Antimicrobial agent	MIC (μg/ml)[a]		
		Range	50%	90%
	Lomefloxacin	4–32	4	16
	Metronidazole	0.125–4	0.5	2
	Sparfloxacin	1–8	2	4
	Temafloxacin	0.5–4	1	2
Bilophila wadsworthia (15)	Amoxicillin-clavulanic acid	4–8	4	8
	Chloramphenicol	2–4	2	4
	Ciprofloxacin	0.25–1	0.25	0.5
	Clindamycin	0.125–>32	0.5	8
	DU-6859	0.25–0.25	0.25	0.25
	Fleroxacin	0.5–2	1	1
	Imipenem	0.062–0.25	0.125	0.25
	Lomefloxacin	0.5–2	1	2
	Metronidazole	0.125–0.125	0.125	0.125
	Sparfloxacin	0.25–1	0.5	0.5
	Temafloxacin	0.25–1	0.5	1
Fusobacterium nucleatum (16)	Amoxicillin-clavulanic acid	0.125–0.5	0.125	0.5
	Chloramphenicol	0.5–4	1	2
	Ciprofloxacin	0.5–4	2	4
	Clindamycin	0.125–0.5	0.125	0.125
	DU-6859	0.062–0.25	0.062	0.062
	Fleroxacin	4–16	8	16
	Imipenem	0.062–0.125	0.062	0.125
	Lomefloxacin	4–8	8	8
	Metronidazole	0.125–0.25	0.125	0.25
	Sparfloxacin	0.5–2	1	2
	Temafloxacin	0.5–2	0.5	1
Fusobacterium mortiferum-Fusobacterium varium group (10)	Amoxicillin-clavulanic acid	2–32	4	4
	Chloramphenicol	0.5–4	0.5	2
	Ciprofloxacin	0.25–32	2	16
	Clindamycin	0.125–16	0.125	8
	DU-6859	0.062–0.5	0.062	0.5
	Fleroxacin	1–64	16	32
	Imipenem	0.25–2	1	2
	Lomefloxacin	1–32	8	32
	Metronidazole	0.125–0.25	0.125	0.25
	Sparfloxacin	0.5–16	1	16
	Temafloxacin	0.25–8	2	8
Other *Fusobacterium* species (12)[g]	Amoxicillin-clavulanic acid	0.125–4	0.125	4
	Chloramphenicol	0.5–4	1	2
	Ciprofloxacin	1–32	2	4
	Clindamycin	0.125–8	0.125	0.125
	DU-6859	0.062–0.5	0.062	0.25
	Fleroxacin	1–>64	8	32
	Imipenem	0.062–1	0.062	0.5
	Lomefloxacin	4–64	8	32
	Metronidazole	0.125–0.5	0.125	0.25
	Sparfloxacin	1–32	2	4
	Temafloxacin	0.5–64	1	8
Clostridium difficile (9)[h]	Amoxicillin-clavulanic acid	0.5–4	2	
	Chloramphenicol	1–32	4	
	Ciprofloxacin	1–16	8	
	Clindamycin	0.25–>32	4	
	DU-6859	0.125–0.25	0.25	
	Fleroxacin	4–32	16	
	Imipenem	0.5–8	8	
	Lomefloxacin	4–32	32	
	Metronidazole	0.125–0.5	0.125	
	Sparfloxacin	0.5–8	8	
	Temafloxacin	1–4	4	
Clostridium perfringens (9)	Amoxicillin-clavulanic acid	0.125–0.25	0.125	
	Chloramphenicol	2–4	4	

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TABLE 1—*Continued*

Microorganism (no. of isolates)	Antimicrobial agent	MIC (μg/ml)[a]		
		Range	50%	90%
	Ciprofloxacin	0.25–1	1	
	Clindamycin	0.125–8	2	
	DU-6859	0.062–0.25	0.062	
	Fleroxacin	0.5–2	1	
	Imipenem	0.062–0.5	0.062	
	Lomefloxacin	1–4	1	
	Metronidazole	0.5–2	1	
	Sparfloxacin	0.25–0.5	0.25	
	Temafloxacin	0.25–0.5	0.25	
Clostridium ramosum (9)	Amoxicillin-clavulanic acid	0.125–1	0.125	
	Chloramphenicol	2–8	4	
	Ciprofloxacin	4–16	8	
	Clindamycin	1–>32	4	
	DU-6859	0.125–0.5	0.5	
	Fleroxacin	8–32	16	
	Imipenem	0.25–1	0.5	
	Lomefloxacin	16–32	32	
	Metronidazole	0.5–2	1	
	Sparfloxacin	2–8	2	
	Temafloxacin	2–4	2	
Other *Clostridium* species (7)[i]	Amoxicillin-clavulanic acid	0.125–4	1	
	Chloramphenicol	2–8	2	
	Ciprofloxacin	0.25–128	4	
	Clindamycin	0.125–32	1	
	DU-6859	0.062–0.5	0.25	
	Fleroxacin	0.25–>64	16	
	Imipenem	0.062–4	1	
	Lomefloxacin	0.25–>64	16	
	Metronidazole	0.125–0.5	0.125	
	Sparfloxacin	0.25–16	2	
	Temafloxacin	0.25–32	2	
Peptostreptococcus species (20)[j]	Amoxicillin-clavulanic acid	0.125–8	0.125	0.5
	Chloramphenicol	1–4	2	2
	Ciprofloxacin	0.25–2	1	2
	Clindamycin	0.125–8	0.125	2
	DU-6859	0.062–0.125	0.062	0.062
	Fleroxacin	2–16	2	8
	Imipenem	0.062–0.25	0.062	0.062
	Lomefloxacin	2–8	4	8
	Metronidazole	0.125–2	0.25	0.5
	Sparfloxacin	0.25–2	0.25	0.5
	Temafloxacin	0.25–1	0.5	1
Gram-positive rods (non-spore forming) (20)[k]	Amoxicillin-clavulanic acid	0.125–16	0.5	1
	Chloramphenicol	0.5–8	4	8
	Ciprofloxacin	0.25–64	2	16
	Clindamycin	0.125–4	0.25	1
	DU-6859	0.062–0.5	0.062	0.25
	Fleroxacin	1–>64	4	64
	Imipenem	0.062–2	0.125	0.5
	Lomefloxacin	1–>64	4	64
	Metronidazole	0.25–>128	>128	>128
	Sparfloxacin	0.25–8	0.5	8
	Temafloxacin	0.25–8	1	4
Total (330)	Amoxicillin-clavulanic acid	0.125–64	1	8
	Chloramphenicol	0.5–32	4	8
	Ciprofloxacin	0.25–128	4	32
	Clindamycin	0.125–>32	0.5	8
	DU-6859	0.062–1	0.125	0.25
	Fleroxacin	0.25–>64	8	32
	Imipenem	0.062–>64	0.125	1
	Lomefloxacin	0.25–>64	8	32
	Metronidazole	0.125–>128	0.5	2
	Sparfloxacin	0.25–32	2	4
	Temafloxacin	0.25–64	1	4

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[a] 50% and 90%, MIC_{50} and MIC_{90}, respectively.
[b] Includes *B. caccae* (3), *B. distasonis* (11), *B. eggerthii* (3), *B. merdae* (1), *B. ovatus* (8), *B. stercoris* (4), *B. thetaiotaomicron* (29), *B. uniformis* (10), and *B. vulgatus* (15).
[c] The current species, *B. gracilis*, is composed of a diverse group of organisms which will probably be divided into two or more species.
[d] Includes *B. ureolyticus* (5), *B. splanchnicus* (5), and *B. capillosus* (2).
[e] Includes *P. asaccharolytica* (4), *P. endodontalis* (2), and *P. gingivalis* (3).
[f] Includes *P. bivia* (3), *P. buccae* (3), *P. corporis* (1), *P. denticola* (1), *P. disiens* (1), *P. intermedia* (5), *P. loescheii* (6), *P. melaninogenica* (4), and *P. oris* (1).
[g] Includes *F. gonidiaformans* (4), *F. naviforme* (1), *F. necrogenes* (1), *F. necrophorum* (3), *F. russii* (1), and *Fusobacterium* sp. (2).
[h] The breakpoint is used only as a reference point. *C. difficile* is primarily of interest in relation to antimicrobial agent-induced pseudomembranous colitis. These data must be interpreted in the context of the level of the drug achieved in the colon and the impact of the agent on indigenous colonic flora.
[i] Includes *C. cadaveris* (1), *C. clostridioforme* (2), *C. innocuum* (1), *C. septicum* (1), *C. sordellii* (1), and *C. sporosphaeroides* (1).
[j] Includes *P. anaerobius* (3), *P. asaccharolyticus* (2), *P. magnus* (3), *P. micros* (11), and *P. tetradius* (1).
[k] Includes *Actinomyces odontolyticus* (1), *Actinomyces* sp. (3), *Eubacterium lentum* (3), *Eubacterium* sp. (1), *Lactobacillus catenaformis* (1), *Lactobacillus jensenii* (1), *Lactobacillus* sp. (5), and *Propionibacterium acnes* (5).

penem-resistant strains of *B. fragilis*. Ciprofloxacin, fleroxacin, and lomefloxacin had virtually no activity against these organisms; sparfloxacin inhibited 65% of the strains at 2 μg/ml, and temafloxacin inhibited 95% of the strains at 4 μg/ml. Amoxicillin-clavulanate, chloramphenicol, imipenem, and metronidazole inhibited >90% of *B. fragilis* and other *B. fragilis* group organisms at their respective breakpoints. The MIC of each of these drugs at which 90% of the strains were susceptible (MIC_{90}) for *B. fragilis* (0.25 μg/ml) was 3 twofold dilutions lower than that of temafloxacin and 7 twofold dilutions lower than that of ciprofloxacin.

DU-6859a was the quinolone most active against strains of other *B. fragilis* group species as well, inhibiting all strains at 1 μg/ml. Values for the other quinolones tested were similar to those obtained with *B. fragilis* organisms. Ciprofloxacin, fleroxacin, and lomefloxacin inhibited approximately half of the strains of other *Bacteroides* species tested; sparfloxacin inhibited 85% of them at 2 μg/ml, and temafloxacin inhibited 92% at 4 μg/ml.

All strains of other gram-negative anaerobes (*B. gracilis*, other *Bacteroides* species, *Porphyromonas* species, *Prevotella* species, *Bilophila wadsworthia*, and *Fusobacterium* species) were inhibited by DU-6859a at 1 μg/ml. Ciprofloxacin inhibited 54, 65, 82, and 50% of the strains of other *Bacteroides* species, *Prevotella* species, *Fusobacterium nucleatum*, and *Fusobacterium mortiferum-F. varium* group species, respectively, at 2 μg/ml.

Gram-positive organisms (*Clostridium* species and the non-spore-forming gram-positive rods) were all inhibited by DU-6859a at 2 μg/ml. The other quinolones were much less active against non-spore-forming gram-positive rods (i.e., 24 to 70% of the strains were inhibited by concentrations of 2 μg/ml). The MIC_{90} of DU-6859a (0.25 μg/ml) was 4 to 8 twofold dilutions lower than those of the other quinolones. All *Peptostreptococcus* strains were inhibited by all of the quinolones at 2 μg/ml with the exception of lomefloxacin and fleroxacin (10 and 60% of the strains inhibited, respectively).

Serious resistance to ciprofloxacin and ofloxacin has developed among *Staphylococcus aureus* and *Pseudomonas aeruginosa* strains. In a series of studies reported at the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy, DU-6859a inhibited many methicillin-resistant, ciprofloxacin-resistant *S. aureus* and *Staphylococcus epidermidis* strains; ciprofloxacin-resistant *P. aeruginosa* strains (1); and norfloxacin-ofloxacin-resistant, methicillin-resistant *S. aureus* strains (3). In other studies, DU-6859a showed more activity against a number of organisms than related compounds did; included in the studies were staphylococci (including methicillin-resistant, quinolone-resistant *S. aureus*), streptococci, and other gram-positive bacteria, including some ciprofloxacin-resistant organisms (8, 11). A large study (5,086 isolates) showed that DU-6859a inhibited 90% of the isolates of *Citrobacter* species, *Enterobacter cloacae*, *Escherichia coli*, *Morganella morganii*, *Proteus mirabilis*, and *Proteus vulgaris* at concentrations of ≤0.06 μg/ml (5).

Other studies have been done with small numbers of anaerobes, and these have yielded results similar to those found in the present study. Marshall and Jones found an MIC_{90} of DU-6859a for *B. fragilis* (26 strains) of 0.5 μg/ml and an MIC_{90} for anaerobic gram-positive bacteria (*Clostridium* and *Peptostreptococcus* strains) of ≤0.12 μg/ml (4). Sato et al. reported an MIC_{50} and an MIC_{90} for *B. fragilis* (23 strains) of 0.1 and 0.39 μg/ml, respectively (8). In this study, DU-6859a inhibited all of the anaerobes tested at ≤1 μg/ml, with an MIC_{90} of 0.25 μg/ml. The excellent in vitro activity of DU-6859a against anaerobes shows promising potential and warrants clinical trials to determine the efficacy of this agent for therapy of infections involving anaerobes.

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