ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2005, p. 3040–3045 Vol. 49, No. 7
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.7.3040–3045.2005

In Vitro Antibacterial Activity of DX-619, a Novel Des-Fluoro(6) Quinolone

Katsuko Fujikawa,* Megumi Chiba, Mayumi Tanaka, and Kenichi Sato

New Product Research Laboratories I, Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan

Received 13 September 2004/Returned for modification 12 December 2004/Accepted 28 March 2005

The in vitro activities of DX-619, des-fluoro(6) quinolone, against 1,208 clinical isolates were examined. DX-619 was particularly potent against staphylococci, including ciprofloxacin- and methicillin-resistant strains; the MIC at which 90% of the strains tested were inhibited was 0.5 μg/ml. In addition, DX-619 was also active against gram-negative bacteria.

The development of resistance to antimicrobial agents and the emergence of multidrug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MRCNS), penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase-producing gram-negative rods, and multidrug-resistant *Pseudomonas aeruginosa* (1, 8, 10, 13, 17, 20), have generated worldwide concern in the medical community. Among these, MRSA and VRE are common gram-positive pathogens of nosocomial infections which account for outbreaks and are increasing in frequency (4, 5, 14). Furthermore, community-acquired MRSA infections have been reported in recent years (6). Vancomycin is still widely used against serious infections caused by MRSA and enterococci, because there are only a few therapeutic options (19). The emergence of vancomycin-resistant strains of MRSA has been reported sporadically since 2002 (2, 9, 18). Recently, linezolid, a new synthetic oxazolidinone active against MRSA and VRE, has been a potential alternative (3, 22). However, linezolid- and vancomycin-resistant enterococci have been reported already (15). These problems reveal an urgent need for new antibacterials that are active against multidrug-resistant gram-positive bacteria. In this context, a novel des-fluoro(6) quinolone, DX-619, has been synthesized, with the chemical structure shown in Fig. 1.

In this study, we compared the antimicrobial activity of DX-619 with those of other quinolones and the other classes of antibacterial agents, including anti-gram-positive bacterial agents, against freshly isolated bacteria.

(This study was presented in part at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill., 14 to 17 September 2003 [H. Inagaki et al., abstr. F-1054].)

DX-619, ciprofloxacin, clinafloxacin, garenoxacin, gatifloxacin, levofloxacin, moxifloxacin, sitafloxacin, and linezolid were synthesized at Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan. Ampicillin, benzylpenicillin, cefaclor, ceftazidime, ceftriaxone, imipenem, oxacillin, arbekacin, clindamycin, metronidazole, minocycline, quinupristin-dalfopristin, teicoplanin, and vancomycin were purchased from the manufacturers or Sigma Aldrich Japan (Tokyo, Japan). Each drug was used as an anhydrous free base.

Bacterial strains were collected by the Levofloxacin Surveillance Group from patients in Japan in 2000 (20), with the exception of the strains mentioned below. *Streptococcus agalactiae*, *Neisseria gonorrhoeae*, *Stenotrophomonas maltophilia*, and anaerobic bacteria isolated in Japan were obtained from BML, Inc. (Saitama, Japan). Five ciprofloxacin-resistant strains of *Streptococcus pneumoniae* were isolated in Asia and Europe in 1997 and 1998 (16), and nine such strains were collected by the Levofloxacin Surveillance Group in Japan in 2002 (21). VRE were obtained from Creighton University (Omaha, Nebr.) and from Kyoto Pharmaceutical University and Gunma University in Japan.

MICs were determined according to the standard agar dilution method recommended by NCCLS (11) for bacterial species other than *Haemophilus influenzae* and anaerobes, for which the agar dilution method recommended by the Japanese Society of Chemotherapy was used (7). Mueller-Hinton agar (Becton Dickinson, Sparks, Md.) supplemented with 5% sheep blood (Kohjin Bio Co., Ltd., Saitama, Japan) was used for streptococci and *Moraxella catarrhalis*, and GC agar (Becton Dickinson) was used for *N. gonorrhoeae*. Mueller-Hinton agar supplemented with 5% Fildes enrichment (Becton Dickinson) was used for *H. influenzae*, and modified Gifu anaerobe medium agar (Nissui Pharmaceutical Co., Ltd., Tokyo, Japan) was used for anaerobic bacteria. Drug-containing agar plates were incubated with one loopful of inoculum, corresponding to about 10^4 CFU (about 10^5 CFU for *S. pneumoniae*) per spot, and were incubated at 35°C for 20 h (48 h for *Peptostreptococcus* spp. and *Clostridium difficile*). *N. gonorrhoeae* was incubated under 5% CO_2, and anaerobic bacteria were incubated

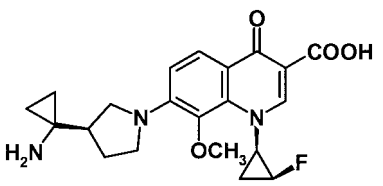

FIG. 1. Chemical structure of DX-619.

* Corresponding author. Mailing address: New Product Research Laboratories I, Daiichi Pharmaceutical Co. Ltd., 16-13 Kitakasai 1-Chome, Edogawa-ku, Tokyo 134-8630, Japan. Phone: 81-3-5696-8236. Fax: 81-3-5696-4264. E-mail: fujikzsl@daiichipharm.co.jp.

TABLE 1. Antibacterial activities of DX-619 and reference compounds against gram-positive bacteria

Organism (no. of strains) and compound	MIC (μg/ml)		
	Range	50%	90%
Staphylococcus aureus			
Methicillin susceptible (48)			
DX-619	≦0.004–0.06	0.008	0.015
Levofloxacin	0.12–8	0.25	0.5
Sitafloxacin	0.008–1	0.03	0.06
Ciprofloxacin	0.12–32	0.5	2
Moxifloxacin	0.03–2	0.06	0.12
Gatifloxacin	0.06–4	0.12	0.25
Garenoxacin	0.008–1	0.03	0.06
Vancomycin	1–2	1	1
Teicoplanin	0.25–1	0.5	0.5
Quinupristin-dalfopristin	0.12–0.25	0.25	0.25
Linezolid	2–4	2	4
Arbekacin	4–128	8	16
Imipenem	0.03–0.06	0.06	0.06
Ceftriaxone	2–16	4	4
Minocycline	0.12–16	0.12	0.12
Oxacillin	0.25–1	0.5	1
Methicillin resistant, ciprofloxacin susceptible (24)			
DX-619	≦0.004–0.015	0.008	0.008
Levofloxacin	0.12–0.25	0.25	0.25
Sitafloxacin	≦0.004–0.03	0.03	0.03
Ciprofloxacin	0.12–0.5	0.5	0.5
Moxifloxacin	0.015–0.06	0.03	0.06
Gatifloxacin	0.03–0.12	0.12	0.12
Garenoxacin	0.008–0.03	0.015	0.03
Vancomycin	1–2	2	2
Teicoplanin	0.25–2	0.5	1
Quinupristin-dalfopristin	0.12–0.5	0.25	0.5
Linezolid	2	2	2
Arbekacin	4–32	16	32
Imipenem	0.25–64	1	32
Ceftriaxone	32–>128	128	>128
Minocycline	0.12–16	0.12	4
Oxacillin	16–>128	64	>128
Methicillin resistant, ciprofloxacin resistant (99)			
DX-619	0.03–1	0.06	0.5
Levofloxacin	4–>128	8	>128
Sitafloxacin	0.25–16	0.5	8
Ciprofloxacin	8–>64	32	>64
Moxifloxacin	1–64	2	32
Gatifloxacin	1–128	4	64
Garenoxacin	0.25–64	1	32
Vancomycin	0.5–2	1	2
Teicoplanin	0.25–4	1	1
Quinupristin-dalfopristin	0.12–4	0.5	0.5
Linezolid	0.5–2	1	1
Arbekacin	4–>128	8	32
Imipenem	1–>128	32	64
Ceftriaxone	>128	>128	>128
Minocycline	0.06–16	8	16
Oxacillin	64–>128	>128	>128
Coagulase-negative staphylococci			
Methicillin susceptible (46)			
DX-619	≦0.004–0.12	0.008	0.015
Levofloxacin	0.12–16	0.25	0.5
Sitafloxacin	0.008–0.25	0.015	0.03
Ciprofloxacin	0.12–32	0.25	0.5
Moxifloxacin	0.03–4	0.12	0.12
Gatifloxacin	0.06–4	0.12	0.25
Garenoxacin	0.015–1	0.03	0.06
Vancomycin	0.5–4	1	2
Teicoplanin	0.12–4	0.5	2
Quinupristin-dalfopristin	0.12–0.25	0.12	0.25
Linezolid	0.5–1	1	1
Arbekacin	1–32	2	8
Imipenem	0.015–0.03	0.03	0.03
Ceftriaxone	0.5–8	1	2
Minocycline	0.06–0.5	0.06	0.12
Oxacillin	0.06–0.25	0.12	0.12
Methicillin resistant (45)			
DX-619	0.008–0.5	0.06	0.12
Levofloxacin	0.25–>128	8	32
Sitafloxacin	0.015–2	0.25	0.5
Ciprofloxacin	0.12–>64	8	64
Moxifloxacin	0.06–64	1	4
Gatifloxacin	0.12–64	2	4
Garenoxacin	0.03–32	1	4
Vancomycin	1–4	2	2
Teicoplanin	0.25–8	1	4
Quinupristin-dalfopristin	0.12–0.25	0.12	0.25
Linezolid	1–2	1	2
Arbekacin	2–64	16	64
Imipenem	0.12–128	32	64
Ceftriaxone	8–>128	32	>128
Minocycline	0.06–16	0.25	8
Oxacillin	2–>128	32	>128
Streptococcus pneumoniae			
Penicillin susceptible (48)			
DX-619	≦0.004–0.03	0.015	0.015
Levofloxacin	0.5–2	1	2
Sitafloxacin	0.03–0.12	0.06	0.06
Ciprofloxacin	0.5–4	1	2
Moxifloxacin	0.12–0.25	0.12	0.25
Gatifloxacin	0.25–0.5	0.25	0.5
Garenoxacin	0.015–0.25	0.06	0.12
Vancomycin	0.25–1	0.5	1
Quinupristin-dalfopristin	0.5–2	1	1
Linezolid	0.5–2	1	2
Imipenem	≦0.004–0.06	0.008	0.015
Ceftriaxone	0.015–1	0.12	0.5
Benzylpenicillin	0.015–0.06	0.03	0.06
Penicillin intermediate and resistant (50)			
DX-619	0.008–0.06	0.03	0.03
Levofloxacin	1–2	1	2
Sitafloxacin	0.03–0.25	0.06	0.12
Ciprofloxacin	1–8	2	4
Moxifloxacin	0.12–0.5	0.25	0.5
Gatifloxacin	0.25–1	0.5	0.5
Garenoxacin	0.03–0.25	0.12	0.12
Vancomycin	0.25–1	0.5	0.5
Quinupristin-dalfopristin	0.5–4	1	1
Linezolid	1–2	1	2
Imipenem	0.12–0.5	0.25	0.5
Ceftriaxone	0.5–2	1	2
Benzylpenicillin	1–4	2	2
Ciprofloxacin resistant (19)			
DX-619	0.015–0.12	0.03	0.12
Levofloxacin	8–32	16	16
Sitafloxacin	0.12–0.5	0.25	0.5
Ciprofloxacin	4–32	16	32
Moxifloxacin	1–4	2	4
Gatifloxacin	2–8	4	8
arenoxacin	0.06–2	0.5	1
Vancomycin	0.12–1	0.5	1
Quinupristin-dalfopristin	0.5–2	1	1
Linezolid	0.25–1	1	1
Imipenem	≦0.004–0.5	0.06	0.25
Ceftriaxone	0.008–4	0.25	1
Benzylpenicillin	≦0.004–4	0.25	4

Continued on following page

TABLE 1—*Continued*

Organism (no. of strains) and compound	MIC (μg/ml)		
	Range	50%	90%
Streptococcus pyogenes (49)			
DX-619	0.008–0.015	0.008	0.015
Levofloxacin	0.25–2	0.5	1
Sitafloxacin	0.015–0.06	0.03	0.06
Ciprofloxacin	0.25–2	0.5	1
Moxifloxacin	0.12–0.5	0.25	0.5
Gatifloxacin	0.25–0.5	0.25	0.5
Garenoxacin	0.06–0.25	0.12	0.25
Vancomycin	0.5–1	0.5	1
Teicoplanin	0.12–0.25	0.25	0.25
Quinupristin-dalfopristin	0.25–0.5	0.5	0.5
Linezolid	0.25–1	0.5	1
Imipenem	≦0.004–0.008	≦0.004	0.008
Ceftriaxone	≦0.004–0.03	0.03	0.03
Benzylpenicillin	≦0.004–0.015	0.015	0.015
Streptococcus agalactiae (19)			
DX-619	0.008–0.12	0.015	0.12
Levofloxacin	0.5–32	1	32
Sitafloxacin	0.06–1	0.06	0.5
Ciprofloxacin	0.5–32	1	32
Moxifloxacin	0.12–8	0.25	8
Gatifloxacin	0.25–8	0.25	8
Garenoxacin	0.06–4	0.12	4
Vancomycin	0.5–2	1	1
Teicoplanin	0.12–0.5	0.5	0.5
Quinupristin-dalfopristin	0.5	0.5	0.5
Linezolid	1–2	1	2
Imipenem	0.015–0.03	0.03	0.03
Ceftriaxone	0.06–0.25	0.12	0.12
Benzylpenicillin	0.06–0.12	0.06	0.12
Enterococcus faecalis			
Vancomycin susceptible (50)			
DX-619	0.03–0.5	0.06	0.25
Levofloxacin	1–128	2	32
Sitafloxacin	0.06–4	0.12	2
Ciprofloxacin	0.5–64	1	64
Moxifloxacin	0.12–16	0.25	8
Gatifloxacin	0.25–32	0.5	16
Garenoxacin	0.12–8	0.25	4
Vancomycin	1–4	1	2
Teicoplanin	0.12–0.5	0.25	0.5
Quinupristin-dalfopristin	4–32	8	16
Linezolid	1–2	2	2
Imipenem	1–4	1	4
Vancomycin resistant (18)			
DX-619	0.015–0.5	0.25	0.5
Levofloxacin	0.5–64	32	64
Sitafloxacin	0.06–4	2	4
Ciprofloxacin	0.25–128	32	64
Moxifloxacin	0.12–32	16	32
Gatifloxacin	0.25–32	16	32
Garenoxacin	0.06–8	4	8
Vancomycin	8–>128	>128	>128
Teicoplanin	0.25–128	64	128
Quinupristin-dalfopristin	0.5–16	8	16
Linezolid	2	2	2
Imipenem	1–128	2	64
Enterococcus faecium			
Vancomycin susceptible (47)			
DX-619	0.03–4	1	2
Levofloxacin	1–128	16	64
Sitafloxacin	0.06–8	1	4
Ciprofloxacin	1–>64	16	64
Moxifloxacin	0.25–64	8	32
Gatifloxacin	0.25–32	16	32
Garenoxacin	0.25–64	8	32
Vancomycin	0.5–2	1	1
Teicoplanin	0.25–2	0.5	1
Quinupristin-dalfopristin	0.25–16	0.5	2
Linezolid	2	2	2
Imipenem	2–>128	>128	>128
Vancomycin resistant (19)			
DX-619	0.06–4	0.25	2
Levofloxacin	2–64	4	64
Sitafloxacin	0.12–8	0.5	8
Ciprofloxacin	1–>128	4	>128
Moxifloxacin	0.5–32	4	32
Gatifloxacin	0.5–32	4	32
Garenoxacin	0.25–32	8	32
Vancomycin	32–>128	>128	>128
Teicoplanin	0.5–64	32	64
Quinupristin-dalfopristin	0.5–4	0.5	2
Linezolid	2	2	2
Imipenem	16–>128	>128	>128
Enterococcus gallinarum			
Vancomycin resistant (13)			
DX-619	0.12–2	1	2
Levofloxacin	2–64	16	64
Sitafloxacin	0.25–8	2	8
Ciprofloxacin	2–>128	128	>128
Moxifloxacin	0.5–32	4	32
Gatifloxacin	0.5–64	8	32
Garenoxacin	0.25–8	2	8
Vancomycin	8–>128	>128	>128
Teicoplanin	0.5–>128	32	>128
Quinupristin-dalfopristin	0.25–2	0.5	2
Linezolid	2	2	2
Imipenem	1–>128	>128	>128
Peptostreptococcus spp. (13)			
DX-619	≦0.004–1	0.06	0.5
Levofloxacin	0.06–32	4	16
Sitafloxacin	0.015–2	0.06	0.5
Ciprofloxacin	0.12–16	2	8
Moxifloxacin	0.03–32	0.25	2
Gatifloxacin	0.03–128	0.12	32
Garenoxacin	0.12–64	1	8
Vancomycin	0.25–4	0.25	1
Teicoplanin	0.06–0.12	0.12	0.12
Quinupristin-dalfopristin	0.25–0.5	0.5	0.5
Linezolid	0.5–1	1	1
Imipenem	≦0.004–1	0.03	0.12
Ceftriaxone	0.06–>128	0.25	4
Clostridium difficile (17)			
DX-619	0.25–32	2	2
Levofloxacin	4–128	64	128
Sitafloxacin	0.25–32	1	2
Ciprofloxacin	16–64	32	64
Moxifloxacin	2–128	32	32
Gatifloxacin	2–64	32	32
Garenoxacin	1–128	32	64
Vancomycin	1–4	2	2
Teicoplanin	0.06–0.25	0.12	0.25
Quinupristin-dalfopristin	1–2	1	2
Linezolid	0.5–4	1	4
Imipenem	8–32	16	16
Ceftriaxone	16–>128	128	>128

TABLE 2. Antibacterial activities of DX-619 and reference compounds against gram-negative bacteria

Organism (no. of strains) and compound	MIC (μg/ml)		
	Range	50%	90%
Haemophilus influenzae			
Ampicillin susceptible (20)			
DX-619	≦0.004–0.008	≦0.004	≦0.004
Levofloxacin	0.008–0.015	0.015	0.015
Sitafloxacin	≦0.004	≦0.004	≦0.004
Ciprofloxacin	≦0.004–0.015	0.008	0.008
Moxifloxacin	≦0.004–0.015	0.008	0.015
Gatifloxacin	≦0.004–0.015	0.008	0.008
Garenoxacin	≦0.004–0.008	≦0.004	0.008
Imipenem	0.06–4	0.5	1
Ceftazidime	0.06–0.5	0.12	0.25
Cefaclor	1–8	2	4
Ampicillin	0.12–0.5	0.25	0.5
β-Lactamase positive, ampicillin resistant (21)			
DX-619	≦0.004–0.008	≦0.004	≦0.004
Levofloxacin	≦0.004–0.015	0.015	0.015
Sitafloxacin	≦0.004	≦0.004	≦0.004
Ciprofloxacin	≦0.004–0.015	0.008	0.008
Moxifloxacin	≦0.004–0.03	0.015	0.015
Gatifloxacin	≦0.004–0.015	0.008	0.008
Garenoxacin	≦0.004–0.015	≦0.004	0.008
Imipenem	0.25–4	1	2
Ceftazidime	0.06–0.5	0.12	0.5
Cefaclor	1–32	8	16
Ampicillin	4–128	16	32
β-Lactamase negative, ampicillin intermediate and resistant (25)			
DX-619	≦0.004–0.015	≦0.004	0.015
Levofloxacin	0.008–0.015	0.015	0.015
Sitafloxacin	≦0.004	≦0.004	≦0.004
Ciprofloxacin	0.008–0.015	0.008	0.015
Moxifloxacin	0.008–0.03	0.015	0.03
Gatifloxacin	≦0.004–0.015	0.008	0.015
Garenoxacin	≦0.004–0.015	0.008	0.015
Imipenem	0.25–8	4	8
Ceftazidime	0.12–1	0.5	0.5
Cefaclor	8–128	64	128
Ampicillin	2–8	4	8
Moraxella catarrhalis (48)			
DX-619	0.008–0.06	0.015	0.03
Levofloxacin	0.03–0.06	0.03	0.06
Sitafloxacin	≦0.004–0.015	0.008	0.015
Ciprofloxacin	0.03–0.06	0.03	0.06
Moxifloxacin	0.03–0.12	0.06	0.06
Gatifloxacin	0.03–0.06	0.03	0.06
Garenoxacin	0.008–0.03	0.015	0.03
Imipenem	0.12–2	1	1
Ceftazidime	0.12–>32	0.5	2
Ampicillin	0.25–8	4	8
Escherichia coli (48)			
DX-619	0.015–8	0.03	1
Levofloxacin	0.015–32	0.06	4
Sitafloxacin	≦0.004–2	0.015	0.5
Ciprofloxacin	≦0.004–64	0.015	4
Moxifloxacin	0.015–32	0.06	8
Gatifloxacin	0.008–16	0.03	4
Garenoxacin	0.015–64	0.06	8
Imipenem	0.06–0.5	0.12	0.25
Ceftazidime	0.06–8	0.25	0.5
Ampicillin	1–>128	4	>128
Klebsiella pneumoniae (49)			
DX-619	0.03–1	0.06	0.12
Levofloxacin	0.015–2	0.06	0.12
Sitafloxacin	≦0.004–0.5	0.03	0.03
Ciprofloxacin	≦0.004–0.5	0.03	0.06
Moxifloxacin	0.06–2	0.12	0.25
Gatifloxacin	0.015–2	0.06	0.12
Garenoxacin	0.06–2	0.12	0.25
Imipenem	0.12–0.5	0.12	0.25
Ceftazidime	0.06–1	0.12	0.25
Ampicillin	1–>128	32	32
Enterobacter spp. (26)			
DX-619	0.03–2	0.06	0.5
Levofloxacin	0.03–2	0.06	0.5
Sitafloxacin	0.015–0.5	0.015	0.12
Ciprofloxacin	0.008–2	0.015	0.25
Moxifloxacin	0.03–4	0.06	0.5
Gatifloxacin	0.03–2	0.03	0.5
Garenoxacin	0.03–8	0.12	1
Imipenem	0.12–1	0.25	1
Ceftazidime	0.12–>128	0.25	64
Citrobacter spp. (26)			
DX-619	0.03–4	0.25	1
Levofloxacin	0.015–4	0.12	0.5
Sitafloxacin	0.008–2	0.06	0.5
Ciprofloxacin	0.008–2	0.03	0.25
Moxifloxacin	0.03–8	0.25	2
Gatifloxacin	0.015–4	0.12	1
Garenoxacin	0.03–16	0.5	4
Imipenem	0.25–1	0.5	1
Ceftazidime	0.12–>128	1	128
Salmonella spp. (26)			
DX-619	0.06–0.25	0.06	0.06
Levofloxacin	0.03–0.12	0.06	0.06
Sitafloxacin	0.015–0.12	0.015	0.015
Ciprofloxacin	0.015–0.12	0.015	0.015
Moxifloxacin	0.06–0.5	0.12	0.12
Gatifloxacin	0.03–0.25	0.06	0.06
Garenoxacin	0.06–0.5	0.06	0.12
Imipenem	0.12–0.25	0.25	0.25
Ceftazidime	0.25–0.5	0.25	0.5
Proteus mirabilis (26)			
DX-619	0.06–4	0.12	2
Levofloxacin	0.03–8	0.06	2
Sitafloxacin	0.015–1	0.03	0.25
Ciprofloxacin	0.015–4	0.03	1
Moxifloxacin	0.25–32	0.5	8
Gatifloxacin	0.06–16	0.12	2
Garenoxacin	0.12–32	0.5	16
Imipenem	0.25–4	1	2
Ceftazidime	0.03–0.25	0.06	0.12
Indole-positive *Proteus* (25)			
DX-619	0.03–8	0.12	0.5
Levofloxacin	0.015–4	0.06	0.25
Sitafloxacin	≦0.004–1	0.015	0.06
Ciprofloxacin	≦0.004–4	0.015	0.06
Moxifloxacin	0.06–32	0.25	0.5
Gatifloxacin	0.03–8	0.12	0.5
Garenoxacin	0.12–128	0.25	2
Imipenem	0.25–4	2	4
Ceftazidime	0.06–16	0.12	0.25
Serratia marcescens (26)			
DX-619	0.12–8	0.5	2
Levofloxacin	0.06–8	0.25	2
Sitafloxacin	0.03–1	0.12	0.5
Ciprofloxacin	0.03–8	0.06	2
Moxifloxacin	0.12–16	0.5	4

Continued on following page

TABLE 2—*Continued*

Organism (no. of strains) and compound	MIC (μg/ml)		
	Range	50%	90%
Gatifloxacin	0.12–8	0.25	2
Garenoxacin	0.5–64	1	4
Imipenem	0.5–2	1	1
Ceftazidime	0.12–16	0.5	4
Pseudomonas aeruginosa			
Ciprofloxacin susceptible (51)			
DX-619	0.25–2	1	1
Levofloxacin	0.25–2	0.5	1
Sitafloxacin	0.03–0.25	0.12	0.25
Ciprofloxacin	0.06–0.5	0.12	0.25
Moxifloxacin	0.5–4	2	2
Gatifloxacin	0.25–2	1	1
Garenoxacin	0.25–4	1	2
Imipenem	0.5–32	2	16
Ceftazidime	0.5–128	2	4
Ciprofloxacin intermediate and resistant (52)			
DX-619	2–>128	16	64
Levofloxacin	4–>128	32	>128
Sitafloxacin	0.5–32	4	16
Ciprofloxacin	2–>64	16	64
Moxifloxacin	8–>128	64	>128
Gatifloxacin	4–>128	32	64
Garenoxacin	8–>128	64	>128
Imipenem	0.5–>128	16	128
Ceftazidime	1–>128	16	>128
Stenotrophomonas maltophilia (20)			
DX-619	0.12–2	0.5	2
Levofloxacin	0.06–4	1	4
Sitafloxacin	0.03–0.5	0.12	0.5
Ciprofloxacin	0.015–8	2	4
Moxifloxacin	0.12–2	0.5	2
Gatifloxacin	0.12–4	1	2
Garenoxacin	0.25–8	2	8
Imipenem	2–>128	>128	>128
Ceftazidime	2–128	32	128
Acinetobacter spp. (26)			
DX-619	0.03–1	0.03	0.12
Levofloxacin	0.06–4	0.12	0.5
Sitafloxacin	0.015–1	0.03	0.12
Ciprofloxacin	0.06–8	0.12	0.5
Moxifloxacin	0.03–2	0.06	0.5
Gatifloxacin	0.03–2	0.06	0.25
Garenoxacin	0.015–2	0.03	0.12
Imipenem	0.12–0.5	0.25	0.5
Ceftazidime	1–16	4	8
Neisseria gonorrhoeae			
Ciprofloxacin susceptible (23)			
DX-619	≦0.004–0.015	≦0.004	0.015
Levofloxacin	≦0.004–0.12	0.008	0.06
Sitafloxacin	≦0.004	≦0.004	≦0.004
Ciprofloxacin	≦0.004–0.06	0.008	0.06
Moxifloxacin	≦0.004–0.06	0.008	0.06
Gatifloxacin	≦0.004–0.03	0.008	0.03
Garenoxacin	≦0.004–0.03	≦0.004	0.015
Imipenem	0.03–2	0.06	0.25
Ceftazidime	0.008–0.25	0.06	0.12
Benzylpenicillin	0.06–1	0.12	0.25
Ciprofloxacin resistant (26)			
DX-619	0.25–2	0.5	1
Levofloxacin	4–16	8	16
Sitafloxacin	0.12–0.5	0.25	0.5
Ciprofloxacin	4–32	16	32
Moxifloxacin	2–8	4	8
Gatifloxacin	1–4	2	4
Garenoxacin	1–8	2	4
Imipenem	0.03–2	1	2
Ceftazidime	0.06–1	0.5	1
Benzylpenicillin	0.06–4	2	4
Bacteroides fragilis (20)			
DX-619	0.06–0.5	0.06	0.5
Levofloxacin	1–32	1	32
Sitafloxacin	0.03–0.5	0.06	0.25
Ciprofloxacin	4–64	4	64
Moxifloxacin	0.25–8	0.25	4
Gatifloxacin	0.25–8	0.5	8
Garenoxacin	0.12–2	0.12	2
Imipenem	0.06–2	0.12	1
Ceftazidime	4–>128	32	>128
Metronidazole	0.25–1	0.5	1
Clindamycin	0.06–>128	0.25	>128

under an anaerobic atmosphere. The MIC was defined as the lowest drug concentration that prevented visible growth of bacteria. Staphylococci, *S. pneumoniae*, enterococci, *H. influenzae*, *P. aeruginosa*, and *N. gonorrhoeae* were classified into three categories, susceptible, intermediate, or resistant, according to the breakpoint of NCCLS standards (12). The quality control strains recommended by NCCLS were included as internal controls throughout the study.

Table 1 shows the antibacterial activity of DX-619 against gram-positive bacteria in comparison with those of reference compounds. The MIC_{90}s (MICs at which 90% of isolates are inhibited) of DX-619 against methicillin-susceptible *Staphylococcus aureus* and methicillin-susceptible coagulase-negative staphylococci were both 0.015 μg/ml. MIC_{90}s of DX-619 against ciprofloxacin-susceptible MRSA, ciprofloxacin-resistant MRSA, and MRCNS were 0.008, 0.5, and 0.12 μg/ml, respectively. Against staphylococci, DX-619 showed the most potent activity among the compounds tested, including anti-gram-positive agents. DX-619 was especially potent against ciprofloxacin-resistant MRSA, inhibiting the growth of all strains at 1 μg/ml, a MIC 2-fold lower than those of vancomycin and linezolid, 4-fold lower than those of teicoplanin and quinupristin-dalfopristin, and at least 16-fold lower than those of the other compounds tested. MIC_{90}s of DX-619 against penicillin-susceptible *S. pneumoniae*, penicillin-resistant *S. pneumoniae*, *Streptococcus pyogenes*, and *S. agalactiae* were 0.015, 0.03, 0.015, and 0.12 μg/ml, respectively. Against 19 strains of ciprofloxacin-resistant *S. pneumoniae*, MICs of DX-619 ranged from 0.015 to 0.12 μg/ml, and the activity was also the highest among the compounds tested. MIC_{90}s of DX-619 against vancomycin-susceptible and -resistant *Enterococcus faecalis* were 0.25 and 0.5 μg/ml, respectively, and MIC_{90}s against vancomycin-susceptible and -resistant *Enterococcus faecium* and vancomycin-resistant *Enterococcus gallinarum*

were all 2 μg/ml. The activity against these VRE was also the highest among the reference compounds. DX-619 inhibited 90% of isolates of *Peptostreptococcus* spp. and *C. difficile* at 0.5 and 2 μg/ml, respectively.

The antibacterial activity of DX-619 against gram-negative strains is shown in Table 2. DX-619 showed good antibacterial activity against *H. influenzae*, including ampicillin-resistant strains, and *M. catarrhalis*, against which the highest MIC was 0.06 μg/ml. DX-619 inhibited 90% of isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Citrobacter* spp., *Salmonella* spp., *Proteus mirabilis*, indole-positive *Proteus*, and *Serratia marcescens* at 1, 0.12, 0.5, 1, 0.06, 2, 0.5, and 2 μg/ml, respectively, and these activities were comparable to those of levofloxacin. DX-619 also showed activity comparable to that of levofloxacin against ciprofloxacin-susceptible *P. aeruginosa*, with a MIC_{90} of 1 μg/ml. The MIC_{90} of DX-619 against ciprofloxacin-resistant *P. aeruginosa* was 64 μg/ml. Against *Acinetobacter* spp. and *N. gonorrhoeae* including ciprofloxacin-resistant strains, DX-619 showed good antibacterial activity; the highest MIC against these species was 2 μg/ml. The MIC_{90} of DX-619 was 0.5 μg/ml against *Bacteroides fragilis*. The MICs of the compounds tested against the reference strains for quality control were reproducible throughout the study.

This study showed that DX-619, a recently discovered desfluoro(6) quinolone, possesses the most potent antibacterial activity among the compounds tested against gram-positive bacteria, including ciprofloxacin-resistant MRSA, MRCNS, VRE, and ciprofloxacin-resistant *S. pneumoniae*. The most common resistant pathogen in hospitals is MRSA, which accounts for outbreaks and is increasing in frequency in many facilities (5). The MIC_{90} of DX-619 for ciprofloxacin-resistant MRSA was 0.5 μg/ml, which was lower than those of linezolid and vancomycin. This finding may be attributable to the high inhibitory activity of DX-619 against altered target enzymes of MRSA (M. Tanaka et al., 43rd ICAAC, abstr. F-1060). The relative potency of DX-619 will be better understood when the human pharmacokinetics are available. Further studies of DX-619 are warranted based on the available data.

We thank T. Otani for valuable comments and critical review of the manuscript.

REFERENCES

1. **Bell, J. M., and J. D. Turnidge.** 2002. High prevalence of oxacillin-resistant *Staphylococcus aureus* isolates from hospitalized patients in Asia-Pacific and South Africa: results from SENTRY Antimicrobial Surveillance Program, 1998–1999. Antimicrob. Agents Chemother. **46:**879–881.
2. **Chang, S., D. M. Sievert, J. C. Hageman, M. L. Boulton, F. C. Tenover, F. P. Downes, S. Shah, J. T. Rudrik, G. R. Pupp, W. J. Brown, D. Cardo, S. K. Fridkin, and the Vancomycin-Resistant *Staphylococcus aureus* Investigative Team.** 2003. Infection with vancomycin-resistant *Staphylococcus aureus* containing the *vanA* resistance gene. N. Engl. J. Med. **348:**1342–1347.
3. **Clemett, D., and A. Markham.** 2000. Linezolid. Drugs **59:**815–827.
4. **Diekema, D. J., B. J. BootsMiller, T. E. Vaughn, R. F. Woolson, J. W. Yankey, E. J. Ernst, S. D. Flach, M. M. Ward, C. L. J. Franciscus, M. A. Pfaller, and B. N. Doebbeling.** 2004. Antimicrobial resistance trends and outbreak frequency in United States hospitals. Clin. Infect. Dis. **38:**78–85.
5. **Georgopapadakou, N. H.** 2002. Infectious disease 2001: drug resistance, new drugs. Drug Resist. Update **5:**181–191.
6. **Herold, B. C., L. C. Immergluck, M. C. Maranan, D. S. Lauderdale, R. E. Gaskin, S. Boyle-Vavra, C. D. Leitch, and R. S. Daum.** 1998. Community-acquired methicillin-resistant *Staphylococcus aureus* in children with no identifiable predisposing risk. JAMA **279:**593–598.
7. **Japan Society of Chemotherapy.** 1981. Method for the determination of minimum inhibitory concentration (MIC) of aerobic bacteria by agar dilution method. Chemotherapy (Tokyo) **29:**76–79. (In Japanese.)
8. **Jones, M. E., R. S. Blosser-Middleton, C. Thornsberry, J. A. Karlowsky, and D. F. Sahm.** 2003. The activity of levofloxacin and other antimicrobials against clinical isolates of *Streptococcus pneumoniae* collected worldwide during 1999–2002. Diagn. Microbiol. Infect. Dis. **47:**579–586.
9. **Kacica, M.** 2004. Vancomycin-resistant *Staphylococcus aureus*—New York, 2004. Morb. Mortal. Wkly. Rep. **53:**322–323.
10. **Mathai, D., R. N. Jones, M. A. Pfaller, and the SENTRY Participant Group North America.** 2001. Epidemiology and frequency of resistance among pathogens causing urinary tract infections in 1,510 hospitalized patients: a report from the SENTRY Antimicrobial Surveillance Program (North America). Diagn. Microbiol. Infect. Dis. **40:**129–136.
11. **National Committee for Clinical Laboratory Standards.** 2001. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard, 5th ed. M7-A5. National Committee for Clinical Laboratory Standards, Wayne, Pa.
12. **National Committee for Clinical Laboratory Standards.** 2003. Performance standards for antimicrobial susceptibility testing; 13th informational supplements. M100-S13. National Committee for Clinical Laboratory Standards, Wayne, Pa.
13. **Nilgate, S., P. Nunthapisud, and A. Chongthaleong.** 2003. Vancomycin-resistant enterococci in King Chulalongkorn Memorial Hospital: a 5-year study. J. Med. Assoc. Thai. **86**(Suppl. 2)**:**S224–S229.
14. **NNIS System.** 2003. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2003, issued August 2003. Am. J. Infect. Control **31:**481–498.
15. **Rahim, S., S. K. Pillai, H. S. Gold, L. Venkataraman, K. Inglima, and R. A. Press.** 2003. Linezolid-resistant, vancomycin-resistant *Enterococcus faecium* infection in patients without prior exposure to linezolid. Clin. Infect. Dis. **36:**E146–E148.
16. **Sahm, D. F., M. E. Jones, M. L. Hickey, D. R. Diakun, S. V. Mani, and C. Thornsberry.** 2000. Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* isolated in Asia and Europe, 1997–1998. J. Antimicrob. Chemother. **45:**457–466.
17. **Schmitz, F. J., A. C. Fluit, A. Brisse, J. Verhoef, K. Kohrer, and D. Milatovic.** 1999. Molecular epidemiology of quinolone resistance and comparative in vitro activities of new quinolones against European *Staphylococcus aureus* isolates. FEMS Immunol. Med. Microbiol. **26:**281–287.
18. **Tenover, F. C., L. M. Weigel, P. C. Appelbaum, L. K. McDougal, J. Chaitram, S. McAllister, N. Clark, G. Killgore, C. M. O'Hara, L. Jevitt, J. B. Patel, and B. Bozdogan.** 2004. Vancomycin-resistant *Staphylococcus aureus* isolate from a patient in Pennsylvania. Antimicrob. Agents Chemother. **48:**275–280.
19. **Watanakunakorn, C.** 1981. The antibacterial action of vancomycin. Rev. Infect. Dis. **3:**S210–S215.
20. **Yamaguchi, K., A. Ohno, F. Kashitani, M. Iwata, and the Levofloxacin Surveillance Group.** 2003. Activity of antimicrobial agents against 8,474 clinical isolates obtained from 37 medical institutions during 2000 in Japan. Jpn. J. Antibiot. **56:**5–24.
21. **Yamaguchi, K., A. Ohno, F. Kashitani, M. Iwata, and the Levofloxacin Surveillance Group.** 2005. In vitro susceptibilities to levofloxacin and various antimicrobial agents of 11,475 clinical isolates obtained from 52 centers in 2002. Jpn. J. Antibiot. **58:**17–44.
22. **Zurenko, G. E., B. H. Yagi, R. D. Schaadt, J. W. Allison, J. O. Kilburn, S. E. Glickman, D. K. Hutchinson, M. R. Barbachyn, and S. J. Brickner.** 1996. In vitro activities of U-100592 and U-100766, novel oxazolidinone antibacterial agents. Antimicrob. Agents Chemother. **40:**839–845.