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Potency and Spectrum of DC-159a Tested Against More Than 800 Recent Clinical Isolates

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ABSTRACT

Background: DC-159a has improved, balanced activity against key Gram-positive and –negative pathogens that may be refractory to marketed fluoroquinolones (FQ). A contemporary (2004-2005) international sample of over 800 strains was used to define spectrum and potency.

Methods: Staphylococci (150), *Enterobacteriaceae* (ETB; 323), non-fermentative Gram-negative bacilli (110; 3 species), enterococci (173), *L. monocytogenes* (LM; 10) and *N. gonorrhoeae* (NG; 60), including defined resistant (R) subsets were susceptibility (S) tested by CLSI methods and interpretive criteria were applied to 19 comparators. DC-159a breakpoint of ≤2 µg/ml was used for comparisons to levofloxacin (LEVO) or ciprofloxacin (CIPRO).

Results: DC-159a (MIC_{50} range, 0.03-0.5 µg/ml) potency against wild-type (WT) ETB was generally 2-fold less than LEVO, but the spectrums were equal at ≤2 µg/ml. Similarly, against R subsets (ESBL, KPC-producers, ceftazidime-R, etc.) of ETB DC-159a activity was equal or slightly superior to LEVO. *P. aeruginosa* had a DC-159a MIC_{90} at 2 µg/ml vs LEVO at 1 µg/ml; and LEVO- and CIPRO-resistant strains also had elevated DC-159a MICs. MSSA and CA-MRSA strains had identical DC-159a MIC_{90} (0.03 µg/ml); 8-fold less than LEVO. DC-159a (MIC_{50}, 0.25-0.5 µg/ml) was 4- to 16-fold more active than LEVO vs CoNS, *S. saprophyticus*, and WT enterococci. Highest DC-159a MICs were 0.015, 0.12 and 1 µg/ml for CIPRO-S, -I and -R strains, respectively. MIC_{90} of DC-159a against NG was 1 µg/ml, 8-fold more active than LEVO.

Organism (no. tested)	DC-159a $MIC_{50/90}$	DC-159a % of ≤ 2 µg/ml	LEVO $MIC_{50/90}$	LEVO % of ≤ 2 µg/ml
Acinetobacter, WT (30)	0.06/0.12	100	0.06/0.25	100
P. aeruginosa, WT (30)	0.5/2	97	0.25/1	100
S. maltophilia (30)	0.12/0.5	93	0.5/2	93
E. coli, WT (20)	0.03/0.12	90	0.03/0.25	90
Enterobacter, WT (20)	0.06/0.5	95	0.03/0.12	95
S. aureus, MSSA (30)	0.03/0.03	100	0.12/0.25	100
S. aureus, MRSA (30), Nosocomial	1/2	97	>8/>8	0
E. faecalis, WT (30)	0.12/4	87	0.5/>8	80
LM (10)	0.25/0.25	100	1/1	100

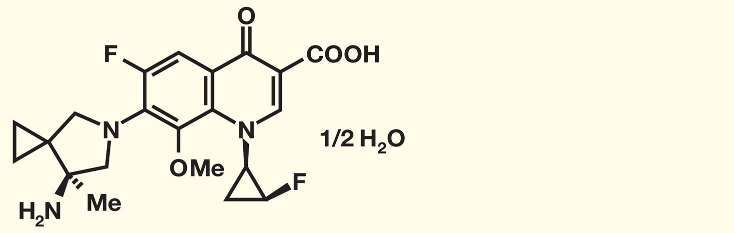
Conclusions: DC-159a activity was particularly noteworthy vs staphylococci (CA-MRSA), WT enterococci, NG (including CIPRO-R strains), and *S. maltophilia* (MIC_{90}, 0.5 µg/ml). Continued development for SSTI, UTI, STD and other indications appears prudent.

INTRODUCTION

Resistances emerging among commonly isolated pathogens have compromised the clinical utility of major classes of antimicrobial agents including the penicillins, cephalosporins, macrolides, aminoglycosides and the fluoroquinolones. Particularly for the fluoroquinolones, the modifications of the DNA gyrase and topoisomerase targets have elevated the MIC values into resistant ranges for gatifloxacin, gemifloxacin, levofloxacin and moxifloxacin among *Streptococcus pneumoniae* (<2% worldwide) and more rarely in other respiratory tract pathogens such as *Haemophilus influenzae* and *Moraxella catarrhalis*. Also, important Gram-positive pathogens (staphylococci, ß-haemolytic streptococci, enterococci) and Gram-negative bacilli (*Enterobacteriaceae*, *Pseudomonas* spp., other non-fermentors) have consistently acquired resistances to the fluoroquinolones via prolonged exposure. An urgent need for novel agents in this class is required to sustain the clinical activity and to provide a balance of potency against emerging pathogen species (examples: *Acinetobacter* spp. and *Stenotrophomonas maltophilia*) while offering continued coverage of the pneumococcus, *S. aureus* and other community-acquired pathogens.

INTRODUCTION (Continued)

Figure 1. Chemical structure of DC-159a.



(+)-7-[(7*S*)-7-amino-7-methyl-5azaspiro[2.4]heptan-5-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluoro-1-cyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid hemihydrate

DC-159a is a novel fluoroquinolone (Figure 1) developed by Daiichi Pharmaceutical Co., Ltd. (Japan) as a candidate oral agent for treatment of commonly isolated community-acquired pathogens. Said to have a wide and potent spectrum of activity, we tested DC-159a against a comprehensive international collection of Gram-positive and -negative pathogens including subsets with defined resistance mechanisms or phenotypes. All tests were performed using reference Clinical and Laboratory Standards Institute (CLSI) methods and interpretations.

MATERIALS AND METHODS

Bacterial Strains: A total of 826 clinical isolates were collected for the study from diverse geographic locations in the Americas, Europe and the Far East. The distribution of strains/species was:

- *Enterobacteriaceae* (323 strains; 30 species)
- *P. aeruginosa* (40 strains)
- *Acinetobacter* spp. (40 strains; 6 species)
- *S. maltophilia* (30 strains)
- *S. aureus* (90 strains; 60 MRSA)
- Coagulase-negative staphylococci (CoNS; 30 strains; 9 oxacillin-resistant)
- *S. saprophyticus* (30 strains)
- *E. faecalis* (65 strains; 30 vancomycin-resistant; 5 linezolid-resistant)
- *E. faecium* (68 strains; 30 vancomycin-resistant; 5 linezolid-resistant)
- Other enterococci (40 strains; 4 species)
- *Listeria monocytogenes* (10 strains)
- *Neisseria gonorrhoeae* (60 strains; 40 ciprofloxacin-non-susceptible)

Specific antimicrobial resistant subsets were tested (see Tables 1-3).

Susceptibility Testing. All tests were performed by CLSI methods: M7-A7 (2006) broth microdilution for all tests except gonococci where the agar dilution method was used with GC agar base and the defined supplement. Category interpretations of MIC results used current M100-S16 (2006) criteria. Quality control (QC) was assured by use of several CLSI-recommended ATCC strains; all QC results were within defined ranges (M100-S16, 2006).

DC-159a was provided by Daiichi and all other comparison agents were obtained from their manufacturers or from Sigma Chemical Co. (St. Louis, MO). Frozen-form broth microdilution panels were produced by JMI Laboratories (North Liberty, IA).

RESULTS

- DC-159a potency was like that of levofloxacin against *Enterobacteriaceae* (Table 1), showing nearly identical percentages of strains inhibited at ≤2 µg/ml (MIC_{50} range, 0.03-0.5 µg/ml).
- Some non-fermentative Gram-negative bacilli were very susceptible to DC-159a (Table 1):
  - *Acinetobacter* spp. MIC_{90} = 0.12 µg/ml
  - *S. maltophilia* MIC_{90} = 0.5 µg/ml (lowest among fluoroquinolones)
  - *P. aeruginosa* MIC_{90} = 2 µg/ml

RESULTS (Continued)

Table 1. Activity of DC-159a tested against 433 strains of Gram-negative bacilli by reference (CLSI) methods.

Organism (no. tested)/antimicrobial agent	MIC (µg/ml): 50%	90%	Range	% by category:[a] Susceptible/Resistant
E. coli				
Wildtype (20)				
DC-159a	0.03	0.12	0.015-8	- / -[b]
Levofloxacin	0.03	0.25	0.015-8	90.0 / 5.0
Gatifloxacin	≤0.03	0.12	≤0.03->4	90.0 / 5.0
Gemifloxacin	0.008	0.06	0.004->2	90.0 / 10.0
Moxifloxacin	≤0.03	0.25	≤0.03->4	- / -
Ciprofloxacin	≤0.03	0.12	≤0.03->4	90.0 / 10.0
Ceftriaxone	≤0.25	≤0.25	≤0.25-16	95.0 / 0.0
Imipenem	≤0.5	≤0.5	≤0.5	100.0 / 0.0
Amikacin	2	2	0.5-4	100.0 / 0.0
ESBL-phenotype (20)[c]				
DC-159a	0.06	>8	0.015->8	- / -
Levofloxacin	0.06	>8	0.015->8	65.0 / 25.0
Gatifloxacin	≤0.03	>4	≤0.03->4	70.0 / 20.0
Gemifloxacin	≤0.03	>1	≤0.03->1	65.0 / 35.0
Moxifloxacin	0.06	>4	≤0.03->4	- / -
Ciprofloxacin	≤0.25	>2	≤0.25->2	65.0 / 35.0
Ceftriaxone	16	>32	1->32	40.0 / 20.0
Imipenem	0.25	0.5	≤0.12-0.5	100.0 / 0.0
Amikacin	2	16	0.5-16	100.0 / 0.0
Klebsiella spp.				
Wildtype (20)[d]				
DC-159a	0.12	1	0.03-8	- / -
Levofloxacin	0.06	1	0.03-8	90.0 / 5.0
Gatifloxacin	0.06	1	≤0.03->4	90.0 / 5.0
Gemifloxacin	0.03	0.5	0.015->2	85.0 / 10.0
Moxifloxacin	0.12	1	0.06->4	- / -
Ciprofloxacin	≤0.03	0.5	≤0.03->4	90.0 / 10.0
Ceftriaxone	≤0.25	32	≤0.25->32	85.0 / 10.0
Imipenem	≤0.5	≤0.5	≤0.5	100.0 / 0.0
Amikacin	1	8	0.5-32	95.0 / 0.0
ESBL-phenotype (20)[e]				
DC-159a	0.5	>8	0.06->8	- / -
Levofloxacin	1	>8	0.03->8	65.0 / 30.0
Gatifloxacin	0.5	>4	≤0.03->4	65.0 / 20.0
Gemifloxacin	0.25	>1	0.015->1	55.0 / 40.0
Moxifloxacin	0.5	>4	0.06->4	- / -
Ciprofloxacin	1	>2	≤0.015->2	55.0 / 40.0
Ceftriaxone	32	>32	4->32	15.0 / 45.0
Imipenem	≤0.5	≤0.5	≤0.5-1	100.0 / 0.0
Amikacin	16	>32	1->32	65.0 / 25.0
KPC-producers (10)[f]				
DC-159a	>8	>8	0.06->8	- / -
Levofloxacin	>8	>8	0.03->8	20.0 / 80.0
Gatifloxacin	>4	>4	≤0.03->4	20.0 / 80.0
Gemifloxacin	>2	>2	0.015->2	10.0 / 90.0
Moxifloxacin	>4	>4	0.06->4	- / -
Ciprofloxacin	>4	>4	≤0.03->4	10.0 / 90.0
Ceftriaxone	>32	>32	16->32	0.0 / 80.0
Imipenem	>8	>8	4->8	10.0 / 60.0
Amikacin	32	>32	4->32	30.0 / 30.0
P. mirabilis (20)[g]				
DC-159a	0.25	>8	0.12->8	- / -
Levofloxacin	0.12	>8	0.03->8	85.0 / 15.0
Gatifloxacin	0.5	>4	0.06->4	75.0 / 20.0
Gemifloxacin	0.25	>2	0.03->2	55.0 / 45.0
Moxifloxacin	1	>4	0.12->4	- / -
Ciprofloxacin	0.12	>2	≤0.03->2	65.0 / 15.0
Ceftriaxone	≤0.25	32	≤0.25->32	80.0 / 10.0
Imipenem	1	2	≤0.5-4	100.0 / 0.0
Amikacin	4	4	2->32	95.0 / 5.0
Citrobacter spp.				
Wildtype (20)[h]				
DC-159a	0.06	0.5	0.03-8	- / -
Levofloxacin	0.03	0.5	0.015-8	90.0 / 5.0
Gatifloxacin	≤0.03	0.5	≤0.03-4	90.0 / 0.0
Gemifloxacin	0.015	0.25	0.004->2	90.0 / 10.0
Moxifloxacin	0.06	1	≤0.03->4	- / -
Ciprofloxacin	≤0.03	0.5	≤0.03->4	90.0 / 10.0
Ceftriaxone	≤0.25	4	≤0.25-8	100.0 / 0.0
Imipenem	≤0.5	1	≤0.5-1	100.0 / 0.0
Amikacin	1	2	0.5-4	100.0 / 0.0
Ceftazidime-resistant (10)[i]				
DC-159a	0.12	1	0.06-2	- / -
Levofloxacin	0.06	1	0.03-4	90.0 / 0.0
Gatifloxacin	0.5	4	≤0.03->4	80.0 / 10.0
Gemifloxacin	0.03	1	0.008-2	70.0 / 20.0
Moxifloxacin	1	>4	0.06->4	- / -
Ciprofloxacin	0.12	4	≤0.03->4	80.0 / 20.0
Ceftriaxone	32	>32	16->32	0.0 / 20.0
Imipenem	≤0.5	1	≤0.5-4	100.0 / 0.0
Amikacin	2	4	1->32	90.0 / 10.0
Enterobacter spp.				
Wildtype (20)[j]				
DC-159a	0.06	0.5	0.03->8	- / -
Levofloxacin	0.03	0.12	0.015->8	95.0 / 5.0
Gatifloxacin	≤0.03	0.12	≤0.03->4	95.0 / 5.0
Gemifloxacin	0.015	0.06	0.008->2	95.0 / 5.0
Moxifloxacin	0.06	0.25	≤0.03->4	- / -
Ciprofloxacin	≤0.03	0.06	≤0.03->4	95.0 / 5.0
Ceftriaxone	≤0.25	0.5	≤0.25->32	95.0 / 5.0
Imipenem	≤0.5	≤0.5	≤0.5-1	100.0 / 0.0
Amikacin	1	2	1-16	100.0 / 0.0
Ceftazidime-resistant (13)[k]				
DC-159a	0.5	8	0.06-8	- / -
Levofloxacin	0.25	>8	0.03->8	76.9 / 23.1
Gatifloxacin	0.5	>4	≤0.03->4	69.2 / 30.8
Gemifloxacin	0.12	>2	0.008->2	76.9 / 23.1
Moxifloxacin	0.5	>4	0.06->4	- / -
Ciprofloxacin	0.25	>4	≤0.03->4	61.5 / 30.8
Ceftriaxone	>32	>32	4->32	23.1 / 61.5
Imipenem	≤0.5	2	≤0.5-4	100.0 / 0.0
Amikacin	2	8	0.5->32	92.3 / 7.7
Indole-positive *Proteae* (40)[l]				
DC-159a	0.25	8	0.06->8	- / -
Levofloxacin	0.06	8	0.03->8	75.0 / 20.0
Gatifloxacin	0.12	>4	≤0.03->4	75.0 / 20.0
Gemifloxacin	0.06	>2	0.004->2	70.0 / 30.0
Moxifloxacin	0.25	>4	0.06->4	- / -
Ciprofloxacin	≤0.03	>4	≤0.03->4	72.5 / 27.5
Ceftriaxone	≤0.25	4	≤0.25-32	92.5 / 0.0
Imipenem	1	2	≤0.5-4	100.0 / 0.0
Amikacin	2	4	0.5-16	100.0 / 0.0
S. marcescens				
Wildtype (20)				
DC-159a	0.5	2	0.12-8	- / -
Levofloxacin	0.12	1	0.06-4	90.0 / 0.0
Gatifloxacin	0.25	2	0.12->4	90.0 / 5.0
Gemifloxacin	0.12	1	0.06->2	75.0 / 20.0
Moxifloxacin	0.5	4	0.25->4	- / -
Ciprofloxacin	0.06	1	0.06->4	90.0 / 10.0
Ceftriaxone	≤0.25	2	≤0.25->32	90.0 / 5.0
Imipenem	≤0.5	1	≤0.5-2	100.0 / 0.0
Amikacin	4	32	1->32	85.0 / 5.0
Ceftazidime-resistant (10)				
DC-159a	2	8	0.25-8	- / -
Levofloxacin	1	8	0.12-8	60.0 / 30.0
Gatifloxacin	2	>4	0.12->4	50.0 / 30.0
Gemifloxacin	1	>2	0.03->2	30.0 / 60.0
Moxifloxacin	2	>4	0.12->4	- / -
Ciprofloxacin	1	>4	0.06->4	50.0 / 50.0
Ceftriaxone	32	>32	16->32	0.0 / 50.0
Imipenem	≤0.5	1	≤0.5-1	100.0 / 0.0
Amikacin	32	>32	2->32	30.0 / 30.0
Salmonella spp.				
Wildtype (20)[m]				
DC-159a	0.06	0.06	0.015-0.25	- / -
Levofloxacin	0.03	0.06	0.015-0.25	100.0 / 0.0
Gatifloxacin	≤0.03	0.06	≤0.03-0.25	100.0 / 0.0
Gemifloxacin	0.015	0.015	0.004-0.12	100.0 / 0.0
Moxifloxacin	0.06	0.12	≤0.03-0.5	- / -
Ciprofloxacin	≤0.03	≤0.03	≤0.03-0.25	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25-16	95.0 / 0.0
Imipenem	≤0.5	≤0.5	≤0.5	100.0 / 0.0
Amikacin	1	2	1-4	100.0 / 0.0
Resistant phenotype (13)[n]				
DC-159a	0.25	0.5	0.06-1	- / -
Levofloxacin	0.25	0.5	0.03-1	100.0 / 0.0
Gatifloxacin	0.12	0.5	≤0.03-1	100.0 / 0.0
Gemifloxacin	0.06	0.25	≤0.008-0.25	100.0 / 0.0
Moxifloxacin	0.25	1	0.03-2	- / -
Ciprofloxacin	0.12	0.25	≤0.03-1	100.0 / 0.0
Ceftriaxone	≤0.25	32	≤0.25-32	70.0 / 0.0
Imipenem	≤0.5	≤0.5	≤0.5	100.0 / 0.0
Amikacin	2	2	1-2	100.0 / 0.0
Shigella spp. (40)[o]				
DC-159a	0.03	0.06	0.015-0.25	- / -
Levofloxacin	0.03	0.06	0.015-0.25	100.0 / 0.0
Gatifloxacin	≤0.03	≤0.03	≤0.03-0.25	100.0 / 0.0
Gemifloxacin	0.008	0.015	0.004-0.12	100.0 / 0.0
Moxifloxacin	≤0.03	0.06	≤0.03-0.25	- / -
Ciprofloxacin	≤0.03	≤0.03	≤0.03-0.25	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 /0.0
Imipenem	≤0.5	≤0.5	≤0.5	100.0 / 0.0
Amikacin	4	4	1-8	100.0 / 0.0
P. aeruginosa				
Wildtype (30)				
DC-159a	0.5	2	0.25-4	- / -
Levofloxacin	0.25	1	0.12-2	100.0 / 0.0
Gatifloxacin	0.5	1	0.12-4	96.7 / 0.0
Moxifloxacin	1	2	0.25-4	- / -
Ciprofloxacin	0.12	0.25	≤0.03-1	100.0 / 0.0
Ceftazidime	2	16	≤1->16	86.7 / 6.7
Cefepime	2	16	1->16	86.7 / 6.7
Imipenem	1	>8	≤0.5->8	83.3 / 13.3
Amikacin	2	4	0.5->32	93.3 / 3.3
Ciprofloxacin-resistant (10)				
DC-159a	>8	>8	4->8	- / -
Levofloxacin	>8	>8	8->8	0.0 / 100.0
Gatifloxacin	>4	>4	4->4	0.0 / 90.0
Moxifloxacin	>4	>4	>4	- / -
Ciprofloxacin	>4	>4	4->4	0.0 / 100.0
Ceftazidime	4	>16	2->16	50.0 / 40.0
Cefepime	16	>16	8->16	40.0 / 20.0
Imipenem	2	>8	≤0.5->8	50.0 / 40.0
Amikacin	8	>32	2->32	60.0 / 40.0
Acinetobacter spp.				
Wildtype (30)[p]				
DC-159a	0.06	0.12	0.015-1	- / -
Levofloxacin	0.06	0.25	0.03-0.5	100.0 / 0.0
Gatifloxacin	≤0.03	0.12	≤0.03-0.5	100.0 / 0.0
Moxifloxacin	≤0.03	0.12	≤0.03-0.25	- / -
Ciprofloxacin	0.12	0.25	0.06-0.5	100.0 / 0.0
Ceftazidime	4	16	≤1->16	76.7 / 10.0
Cefepime	2	16	0.25->16	86.7 / 6.7
Imipenem	≤0.5	≤0.5	≤0.5-4	100.0 / 0.0
Amikacin	2	8	≤0.25->32	93.3 / 6.7
Trim/sulfa	≤0.5	≤0.5	≤0.5->2	93.3 / 6.7
Ciprofloxacin- and levofloxacin-resistant (10)[q]				
DC-159a	8	>8	4->8	- / -
Levofloxacin	>8	>8	8->8	0.0 / 100.0
Gatifloxacin	>4	>4	4->4	0.0 / 90.0
Moxifloxacin	>4	>4	>4	- / -
Ciprofloxacin	>4	>4	>4	0.0 / 100.0
Ceftazidime	>16	>16	8->16	10.0 / 80.0
Cefepime	16	>16	16->16	0.0 / 50.0
Imipenem	1	>8	≤0.5->8	80.0 / 20.0
Amikacin	16	>32	4->32	50.0 / 40.0
Trim/sulfa	>2	>2	>2	0.0 / 100.0
S. maltophilia (30)				
DC-159a	0.12	0.5	0.03-4	- / -
Levofloxacin	0.5	2	0.06->8	93.3 / 6.7
Gatifloxacin	0.5	2	0.12->4	90.0 / 6.7
Moxifloxacin	0.25	1	≤0.03->4	- / -
Ciprofloxacin	1	4	0.25->4	53.3 / 16.7
Ceftazidime	8	>16	≤1->16	50.0 / 43.3
Cefepime	>16	>16	4->16	20.0 / 56.7
Amikacin	>32	>32	4->32	6.7 / 86.7
Trim/sulfa	≤0.5	>2	≤0.5->2	83.3 / 16.7

a. Criteria as published by the CLSI (2006).
b. - = no breakpoint criteria have been established for this category.
c. Includes strains harbouring: TEM-1, -3, -4, -5, -6, -7 and -8, or SHV-5, or CTX-M2, or CMY-2 (8), or FOX-5 (3).
d. Includes: *Klebsiella oxytoca* (5 strains) and *K. pneumoniae* (15 strains).
e. Includes: *Klebsiella pneumoniae* (20 strains) with mobile Amp-C enzymes (9), CTX-M2 (4), SHV-5 (5), SHV-7, and ESBL NOS.
f. Includes: *Klebsiella pneumoniae* (10 strains) harbouring KPC-NOS (4), KPC-2 (5) or KPC-3 (11).
g. CTX-M phenotypes (2).
h. Includes: *Citrobacter braakii* (1 strain), *Citrobacter farmeri* (1 strain), *C. freundii* (11 strains), and *C. koseri* (7 strains).
i. Includes: *Citrobacter freundii* (9 strains) and *Citrobacter species* (1 strain).
j. Includes: *Enterobacter aerogenes* (4 strains), and *E. cloacae* (16 strains).
k. Includes: *Enterobacter aerogenes* (1 strain), *E. cloacae* (10 strains), *E.gergoviae* (1 strain), and *Enterobacter species* (1 strain).
l. Includes: *Morganella morganii* (10 strains), *Proteus vulgaris* (11 strains), *Providencia rettgeri* (9 strains), and *P. stuartii* (10 strains).
m. Includes: *Salmonella group B* (3 strains), *Salmonella group C* (2 strains), *Salmonella group D* (2 strains), *Salmonella species* (8 strains), *S. typhi* (2 strains), and *S. typhimurium* (3 strains).
n. Resistances to ampicillin or cephalosporins or tetracyclines or trimethoprim/sulfamethoxazole. Includes: *Salmonella enteritidis* (1 strain), *Salmonella group B* (1 strain), *Salmonella group C* (1 strain), *S. hadar* (1 strain), *S. heidelberg* (1 strain), *S. typhi* (1 strain), *S. typhimurium* (3 strains), and *S. virchow* (1 strain).
o. Includes: *Shigella boydii* (4 strains), *S. dysenteriae* (3 strains), *S. flexneri* (14 strains), *S. sonnei* (16 strains), and *Shigella species* (3 strains).
p. Includes: *Acinetobacter anitratus* (1 strain), *A. baumannii* (14 strains), *A.calcoaceticus* (3 strains), *A. junii* (2 strains), *A. lwoffii* (8 strains), and *Acinetobacter species* (2 strains).
q. Includes: *Acinetobacter baumannii* (9 strains) and *A. lwoffii* (1 strain).

Note: Also tested and not shown were *Edwardsiella tarda* (1 strain), *Escherichia vulneris* (2 strains), *Hafnia alvei* (4 strains), *Leclercia adecarboxylata* (1 strain), *Pantoea agglomerans* (1 strain), and *Serratia plymuthica* (1 strain).

Table 2. Antimicrobial activity of DC-159a tested against 333 strains of Gram-positive species isolates by CLSI methods.

Organism (no. tested)/antimicrobial agent	MIC (µg/ml): 50%	90%	Range	% by category:[a] Susceptible/Resistant
S. aureus[a]				
Oxacillin-susceptible (30)				
DC-159a	0.03	0.03	0.015-0.06	- / -
Levofloxacin	0.12	0.25	0.06-0.25	100.0 / 0.0
Gatifloxacin	0.06	0.12	≤0.03-0.12	100.0 / 0.0
Moxifloxacin	≤0.03	0.06	≤0.03-0.12	100.0 / 0.0
Ciprofloxacin	0.25	0.5	0.06-0.5	100.0 / 0.0
Ceftriaxone	2	4	1-4	100.0 / 0.0
Imipenem	≤0.5	≤0.5	≤0.5	100.0 / 0.0
Gentamicin	≤2	≤2	≤2-8	96.7 / 0.0
Vancomycin	1	1	0.5-2	100.0 / 0.0
Linezolid	1	2	0.5-2	100.0 / -
Quin/dalfo	≤0.25	0.5	≤0.25->2	96.7 / 3.3
Tetracycline	≤2	4	≤2->8	90.0 / 10.0
Trim/sulfa	≤0.5	≤0.5	≤0.5	100.0 / 0.0
Clindamycin	0.12	0.12	≤0.06-0.5	100.0 / 0.0
Erythromycin	0.25	>8	0.25->8	83.3 / 16.7
Oxacillin-resistant, nosocomial (30)				
DC-159a	1	2	0.5-4	- / -
Levofloxacin	>8	>8	4->8	0.0 / 100.0
Gatifloxacin	4	>4	1->4	0.0 / 96.7
Moxifloxacin	2	4	1->4	0.0 / 83.3
Ciprofloxacin	>4	>4	>4	0.0 / 100.0
Gentamicin	≤2	>8	≤2->8	53.3 / 46.7
Vancomycin	1	2	0.5->16	93.3 / 3.3
Linezolid	1	2	1-2	100.0 / -
Quin/dalfo	0.5	1	≤0.25-1	100.0 / 0.0
Tetracycline	≤2	>8	≤2->8	80.0 / 20.0
Trim/sulfa	≤0.5	>2	≤0.5->2	86.7 / 13.3
Clindamycin	>8	>8	≤0.06->8	26.7 / 70.0
Erythromycin	>8	>8	0.25->8	6.7 / 93.3
Oxacillin-resistant, community-acquired (30)				
DC-159a	0.03	0.03	0.008-0.5	- / -
Levofloxacin	0.12	0.25	0.12-4	93.3 / 6.7
Gatifloxacin	0.06	0.12	≤0.03-2	93.3 / 6.7
Moxifloxacin	≤0.03	0.06	≤0.03-1	93.3 / 0.0
Ciprofloxacin	≤0.25	0.5	≤0.25->4	93.3 / 6.7
Gentamicin	≤2	≤2	≤2-4	100.0 / 0.0
Vancomycin	1	1	0.5-1	100.0 / 0.0
Linezolid	2	2	1-2	100.0 / -
Quin/dalfo	≤0.25	0.5	≤0.25-0.5	100.0 / 0.0
Tetracycline	≤4	≤4	≤4->8	90.0 / 10.0
Trim/sulfa	≤0.5	≤0.5	≤0.5	100.0 / 0.0
Clindamycin	0.12	0.12	≤0.06-0.25	100.0 / 0.0
Erythromycin	>8	>8	>8	0.0 / 100.0
CoNS (30)[b]				
DC-159a	0.06	0.5	0.03-0.5	- / -
Levofloxacin	0.25	8	0.12-8	60.0 / 26.7
Gatifloxacin	0.25	2	0.06-4	60.0 / 16.7
Moxifloxacin	0.25	2	≤0.03-4	63.3 / 16.7
Ciprofloxacin	0.5	>4	0.12->4	56.7 / 43.3
Gentamicin	≤2	8	≤2->8	83.3 / 10.0
Vancomycin	1	2	0.25-2	100.0 / 0.0
Linezolid	1	1	0.5-2	100.0 / -
Quin/dalfo	≤0.25	0.5	≤0.25-1	100.0 / 0.0
Tetracycline	≤2	>8	≤2->8	86.7 / 13.3
Trim/sulfa	≤0.5	>2	≤0.5->2	66.7 / 33.3
Clindamycin	≤0.06	>8	≤0.06->8	83.3 / 16.7
Erythromycin	0.25	>8	≤0.06->8	53.3 / 43.3
Oxacillin	2	>2	≤0.25->2	30.0 / 70.0
S. saprophyticus (30)				
DC-159a	0.12	0.25	0.03-0.5	- / -
Levofloxacin	0.5	2	0.12-8	86.7 / 10.0
Gatifloxacin	0.25	2	0.06-2	83.3 / 13.3
Moxifloxacin	0.12	1	≤0.03-2	83.3 / 6.7
Ciprofloxacin	0.5	>4	0.12->4	83.3 / 16.7
Gentamicin	≤2	8	≤2->8	83.3 / 6.7
Vancomycin	1	2	0.5-2	100.0 / 0.0
Linezolid	1	2	0.5-2	100.0 / -
Quin/dalfo	0.5	1	≤0.25-2	96.7 / 0.0
Tetracycline	≤2	>8	≤2->8	76.7 / 23.3
Trim/sulfa	≤0.5	>2	≤0.5->2	86.7 / 13.3
Clindamycin	≤0.06	0.5	≤0.06->8	90.0 / 10.0
Erythromycin	0.25	>8	0.12->8	60.0 / 40.0
Oxacillin	1	>2	0.5->2	0.0 / 100.0
E. faecalis				
Vancomycin-susceptible (30)				
DC-159a	0.12	4	0.06->8	- / -
Levofloxacin	0.5	>8	0.25->8	80.0 / 20.0
Gatifloxacin	0.25	>4	0.12->4	80.0 / 20.0
Moxifloxacin	0.25	>4	0.06->4	- / -
Ciprofloxacin	0.5	>4	0.25->4	80.0 / 20.0
Ampicillin	≤1	2	≤1-4	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0
Linezolid	1	2	0.5-2	100.0 / 0.0
Gentamicin-HL	≤500	>1000	≤500->1000	70.0 / 30.0
Tetracycline	>8	>8	≤2->8	23.3 / 76.7
Erythromycin	2	>8	0.25->8	13.3 / 46.7
Vancomycin-resistant (30)				
DC-159a	4	4	0.12-8	- / -
Levofloxacin	>8	>8	0.5->8	6.7 / 93.3
Gatifloxacin	>4	>4	0.12->4	6.7 / 93.3
Moxifloxacin	>4	>4	0.12->4	- / -
Ciprofloxacin	>4	>4	0.5->4	6.7 / 93.3
Ampicillin	2	4	≤1-16	96.7 / 3.3
Teicoplanin	≤2	>16	≤2->16	53.3 / 43.3
Linezolid	1	2	1-2	100.0 / 0.0
Gentamicin-HL	>1000	>1000	≤500->1000	30.0 / 70.0
Tetracycline	>8	>8	≤2->8	33.3 / 66.7
Erythromycin	>8	>8	2->8	0.0 / 96.7
E. faecium				
Vancomycin-susceptible (31)				
DC-159a	1	>8	0.06->8	- / -
Levofloxacin	2	>8	0.25->8	51.6 / 45.2
Gatifloxacin	2	>4	0.25->4	51.6 / 45.2
Moxifloxacin	2	>4	0.12->4	- / -
Ciprofloxacin	4	>4	0.25->4	25.8 / 58.1
Ampicillin	>16	>16	≤1->16	41.9 / 58.1
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0
Linezolid	2	2	1-2	100.0 / 0.0
Gentamicin-HL	≤500	>1000	≤500->1000	77.4 / 22.6
Tetracycline	≤2	>8	≤2->8	58.1 / 38.7
Erythromycin	>8	>8	0.25->8	6.5 / 67.7
Vancomycin-resistant (32)				
DC-159a	8	>8	0.25->8	- / -
Levofloxacin	>8	>8	2->8	18.8 / 81.3
Gatifloxacin	>4	>4	0.5->4	18.8 / 81.3
Moxifloxacin	>4	>4	0.5->4	- / -
Ciprofloxacin	>4	>4	1->4	3.1 / 87.5
Ampicillin	>16	>16	2->16	3.1 / 96.9
Teicoplanin	16	>16	≤2->16	46.9 / 50.0
Linezolid	2	2	1-2	100.0 / 0.0
Gentamicin-HL	≤500	>1000	≤500->1000	65.6 / 34.4
Tetracycline	>8	>8	≤2->8	40.6 / 59.4
Erythromycin	>8	>8	1->8	0.0 / 87.5
Enterococcus spp.[c]				
Linezolid-resistant (10)				
DC-159a	4	>8	2->8	- / -
Levofloxacin	>8	>8	>8	0.0 / 100.0
Gatifloxacin	>4	>4	>4	0.0 / 100.0
Moxifloxacin	>4	>4	>4	- / -
Ciprofloxacin	>4	>4	>4	0.0 / 100.0
Ampicillin	≤1	>16	≤1->16	50.0 / 50.0
Vancomycin	>16	>16	0.5->16	40.0 / 60.0
Teicoplanin	>16	>16	≤2->16	40.0 / 60.0
Gentamicin-HL	≤500	>1000	≤500->1000	60.0 / 40.0
Tetracycline	>8	>8	≤2->8	30.0 / 70.0
Erythromycin	>8	>8	2->8	0.0 / 90.0

a. Criteria as published by CLSI (2006), ß-lactam susceptibility should be directed by the oxacillin test results.
b. Includes: *Staphylococcus auricularis* (4 strains), *S. capitis* (3 strains), Staphylococcus coagulase negative (1 strain), *S. cohnii* (1 strain), *S. epidermidis* (5 strains), *S. haemolyticus* (3 strains), *S. hominis* (2 strains), *S. intermedius* (2 strains), *S. lugdunensis* (2 strains), *S. schleiferi* (1 strain), *S. sciuri* (1 strain), *S. simulans* (1 strain), *S. warnerii* (2 strains), and *S. xylosis* (2 strains).
c. Includes: *Enterococcus faecalis* (5 strains) and *E. faecium* (5 strains).

Note: Also tested and not shown were: *E. avium* (10 strains), *E.casseliflavus* (10 strains), *E.gallinarum* (10 strains), *E. raffinosus* (10 strains), and *Listeria moncytogenes* (10 strains).

RESULTS (Continued)

Table 3. Activity of DC-159a tested against *N. gonorrhoeae* strains (60) by the reference agar dilution method.

Organism (no. tested)/antimicrobial agent	MIC (µg/ml): 50%	90%	Range	% by category:[a] Susceptible/Resistant
Ciprofloxacin-susceptible (20)				
DC-159a	0.015	0.015	0.008-0.015	- / -[b]
Levofloxacin	0.015	0.03	0.008-0.03	- / -
Ciprofloxacin	≤0.008	0.015	≤0.008-0.015	100.0 / 0.0
Ceftriaxone	≤0.008	0.015	≤0.008-0.06	100.0 / -
Penicillin	0.25	1	0.015->4	35.0 / 10.0
Tetracycline	0.25	1	0.12-2	55.0 / 10.0
Ciprofloxacin-intermediate (25)				
DC-159a	0.12	0.12	0.03-0.12	- / -
Levofloxacin	0.25	0.5	0.12-0.5	- / -
Ciprofloxacin	0.25	0.5	0.12-0.5	0.0 / 0.0
Ceftriaxone	0.03	0.06	≤0.008-0.12	100.0 / -
Penicillin	2	>4	0.5->4	0.0 / 88.0
Tetracycline	1	2	0.5-2	0.0 / 48.0
Ciprofloxacin-resistant (15)				
DC-159a	1	1	0.25-1	- / -
Levofloxacin	4	8	2-8	- / -
Ciprofloxacin	>4	>4	2->4	0.0 / 100.0
Ceftriaxone	0.015	0.06	≤0.008-0.06	100.0 / -
Penicillin	2	>4	1->4	0.0 / 80.0
Tetracycline	2	>4	0.25->4	6.7 / 73.3

a. Criteria as published by the CLSI (2006).
b. - = no breakpoint criteria have been established for this category.

- Ciprofloxacin- or levofloxacin-resistant stains were also less susceptible to DC-159a; and strains among various resistant subsets showed some co-resistance with DC-159a.
- DC-159a was generally 16-fold more potent than ciprofloxacin against staphylococci and showed potential coverage of many QRDR mutants (Table 2) associated with oxacillin-resistant strains (MIC_{90}, 0.25-2 µg/ml).
- DC-159a had the lowest MIC values among tested fluoroquinolones versus enterococci, but was less active against the vancomycin- and linezolid-resistant strains.
- *N. gonorrhoeae* strains were significantly (two- to eight-fold) more susceptible to DC-159a than levofloxacin with ciprofloxacin-resistant strains having a MIC_{90} of only 1 µg/ml (also the highest recorded MIC).

CONCLUSIONS

- DC-159a demonstrates high potency, superior to comparison class agents, against staphylococci, enterococci, *S. maltophilia* and gonococci.
- DC-159a maintained comparable spectrum and potency to that of levofloxacin against *Enterobacteriaceae*, *P. aeruginosa* and *Acinetobacter* spp.
- Persisting DC-159a activity against strains having QRDR mutation phenotypes warrants further development of this agent.

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