In Vitro Activity of KPI-10 Tested Against Pathogens Commonly Associated with Urinary Tract Infections (UTIs)

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Abstract

Background: KPI-10, formerly WQ-3813, is an investigational fluoroquinolone (FQ) with potent activity against Gram-positive (GP) and -negative (GN) bacteria including select FQ-resistant (FQR) strains. In this study, KPI-10 and comparator FQ were evaluated against contemporary bacterial isolates commonly associated with UTIs.

Methods: Isolates were collected from medical centers in North America (NA) and Europe (EU) during 2008-2010. MIC values were determined using CLSI reference broth microdilution method. QC organisms and interpretive criteria for comparator compounds were those recommended by CLSI.

Results: A total of 614 organisms (NA, 335; EU, 279), 87.3% of which were isolated in 2010, were evaluated. KPI-10 was the only FQ that retained potent activity against FQR *E. coli* (MIC$_{90}$ for all *E. coli*, 2 µg/ml). However, based on MIC$_{50}$ values ciprofloxacin was two- to four-fold more potent than KPI-10 and levofloxacin against wild-type *Klebsiella* spp., *Enterobacter* spp. and *E. coli*. Against *Acinetobacter* spp., KPI-10 activity (MIC$_{90}$, 1 µg/ml) was more than eight-fold greater than that of other FQ. The KPI-10 MIC$_{90}$ value for the FQR subset of *Acinetobacter* spp. was 2 µg/ml. KPI-10 was four-fold less active than ciprofloxacin when tested against *P. aeruginosa* (MIC$_{50,}$ 0.5 versus 0.12 µg/ml). It was two- to eight-fold more potent, and four- to 16-fold more potent, respectively, based on MIC$_{50/90}$ values for the β-haemolytic streptococci and *S. saprophyticus* when compared to other FQ. For *E. faecalis,* KPI-10 was two-fold more potent than ciprofloxacin or levofloxacin and two-fold less potent than moxifloxacin based on the MIC$_{50}$ value, but at least four-fold more active than other fluoroquinolones using the MIC$_{90}$ value.

Conclusions: KPI-10 was the most active FQ tested against GP organism groups and among the most active for GN. Its overall potent activity including activity against select groups of FQR organisms suggests that it merits clinical evaluation for use in UTI including UTI due to emerging FQR *E. coli*.

Introduction

The rising incidence of urinary tract infections (UTI) due to multidrug-resistant (MDR) Gram-negative bacteria has become a major clinical challenge. Of particular concern is rising MDR, including fluoroquinolone resistance, among common Gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter* spp. In terms of overall prevalence, *E. coli* is the most frequent species isolated in complicated and uncomplicated UTI. In UTI, in addition to *E. coli*, other Enterobacteriaceae such as *Klebsiella* spp., *Serratia* spp., *Citrobacter* spp., and *Enterobacter* spp. and nonfermenters such as *Pseudomonas aeruginosa* and Gram-positive cocci, including coagulase-negative staphylococci and *Enterococcus* species are isolated. Treatment of MDR strains has become limited, with the need for empiric broad-spectrum parenteral agents and a lack of oral antimicrobial options.

Fluoroquinolones are one of the most commonly used antibiotic classes for therapy for a variety of human infections, including complicated and uncomplicated urinary tract infections. However, the emergence of resistance to this class has limited its use in infections including those in the urinary tract. In a recent survey of susceptibility results by Sanchez et. al. (*n* = 12,253,679) for urinary *E. coli* isolates obtained from outpatients in the United States from 2000 to 2010, the greatest increase in resistance among isolates obtained from all outpatients was observed for ciprofloxacin (from 3% in 2000 to 17.1% in 2010).

Resistance usually occurs spontaneously due to point mutations in DNA gyrase and DNA topoisomerase IV, often in combination with decreased expression of outer membrane porins and overexpression of multidrug efflux pump systems. In addition, plasmid-mediated quinolone resistance genes have been recognized in the last decade, and these determinants can be found in members of the Enterobacteriaceae.

KPI-10 (formerly WQ-3813, the maelic acid salt of WQ-3810) is a novel fluoroquinolone containing a 6-amino-3,5-difluoropyridine at the 1-position and 3-isopropylaminoazetidine at the 7-position which has potent activity against Gram-positive and -negative bacteria including select strains that are resistant to the currently available fluoroquinolones. In this study, KPI-10 and comparator fluoroquinolones were evaluated against contemporary bacterial isolates commonly associated with urinary tract infections.

Materials & Methods

Bacterial genera and species commonly associated with urinary tract infections were randomly selected from a collection of isolates from medical centers from the SENTRY Antimicrobial Surveillance Program. A total of 614 isolates including Enterobacteriaceae, *P. aeruginosa*, *Acinetobacter* spp., *Staphylococcus saprophyticus*, *Enterococcus* spp. and β-haemolytic streptococci were randomly selected.

Isolates were selected from North American (NA) and European (EU) medical centers during 2008 (5.4%), 2009 (7.3%) and 2010 (87.3%). Isolates included the following species (number of strains, by region): *Escherichia coli* (164), NA (102) and EU (62); *Klebsiella* spp. (54), NA (32) and EU (22); *Enterobacter* spp. (51), NA (31) and EU (20); *Citrobacter* spp. (34), NA (12) and EU (22); *P. mirabilis* (43), NA (21) and EU (22); Indole-positive *Proteae* (44), NA (22) and EU (22); *P. aeruginosa* (43), NA (22) and EU (21); *Acinetobacter* spp. (21 [includes 18 *Acinetobacter baumannii*, 1 *Acinetobacter lwoffii*, and 2 unspeciated *Acinetobacter* strains]), NA (9) and EU (12); *Enterococcus* spp. (72), NA (41) and EU (31) includes *E. faecalis* (45) and *E. faecium* (24); β-haemolytic streptococci (55), NA (32) and EU (23); *S. saprophyticus* (33), NA (11) and EU (22).

KPI-10 antimicrobial powder was provided by Kalidex. The antimicrobial powder was dissolved in distilled water to make a stock solution for testing of 1280 µg/ml. Comparator agent powder lots were provided by JMI Laboratories through Sigma-Aldrich or respective manufacturers. Antimicrobials tested for Gram-positive bacteria were KPI-10, ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin, erythromycin, clindamycin, cefepime, meropenem, linezolid, and vancomycin. For Gram-negative bacteria, KPI-10, ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin, ceftazidime, cefepime,meropenem, piperacillin/tazobactam, amikacin, and tigecycline were tested. MIC values were determined using the reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution method as described in M07-A9 [2012]. Reference frozen-form assay panels were produced by JMI Laboratories (North Liberty, Iowa, USA) and consisted of two media types; cation-adjusted Mueller-Hinton broth (MHB), and MHB plus 2.5-5% lysed horse blood. Quality control (QC) ranges and interpretive criteria for comparator compounds were as published in CLSI M100-S22 [2012]; tested QC strains *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619. All QC results were within CLSI established ranges.

Results

- The MIC distributions for KPI-10 and comparator fluoroquinolones are located in Table 1. The activity of KPI-10 and comparator agents against select Gram-negative and -positive commonly isolated UTI pathogens are presented in Tables 2 and 3, respectively.
- Gram-negative bacteria
  - Enterobacteriaceae
    - *Escherichia coli* (n=164). Tigecycline was the most potent agent against *E. coli* with a MIC$_{90}$ value at 0.25 µg/ml for all isolates. KPI-10 exhibited a MIC$_{90}$ value at 2 µg/ml which was four-fold greater than the other fluoroquinolones. KPI-10 was more potent than ciprofloxacin against ciprofloxacin-resistant isolates. The highest KPI-10 MIC value was 4 µg/ml (seven isolates) while for ciprofloxacin there were 46 isolates with MIC values ≥4 µg/ml. For the ciprofloxacin-resistant subset of 46 *E. coli* the KPI-10 MIC$_{50/90}$ value was 1/4 µg/ml while for ciprofloxacin the MIC$_{50/90}$ value was >8/>8 µg/ml.
    - *Enterobacter* spp. (n=51). Ciprofloxacin was the most potent agent with a MIC$_{90}$ value of 0.25 µg/ml for all isolates. KPI-10, levofloxacin, gatifloxacin,and tigecycline demonstrated MIC$_{90}$ values at 0.5 µg/ml.
    - *Klebsiella* spp. (n=54). Tigecycline and amikacin were the most potent agents with MIC$_{90}$ values of 0.5 and 2 µg/ml, respectively. The MIC$_{90}$ values for the fluoroquinolones ranged from 8 µg/ml for gatifloxacin to >8 µg/ml for KPI-10, levofloxacin, ciprofloxacin, and moxifloxacin.
    - *P. mirabilis* (n=43). The most potent agents were the β-lactams, ceftazidime, cefepime, meropenem, and piperacillin-tazobactam with MIC$_{90}$ values of ≤0.5 µg/ml. KPI-10 was the most potent fluoroquinolone with a MIC$_{90}$ value of 4 µg/ml. The other fluoroquinolones had MIC$_{90}$ values at 8->8 µg/ml.
  - Non-fermenters
    - *Pseudomonas aeruginosa* (n=43). Meropenem was the most potent agent with a MIC$_{90}$ value of 4 µg/ml. The MIC$_{90}$ values for KPI-10 and the other fluoroquinolones including ciprofloxacin and levofloxacin were >8 µg/ml. The MIC$_{50}$ value for ciprofloxacin was 0.12 µg/ml and for KPI-10, levofloxacin and gatifloxacin was 0.5 µg/ml.
    - *Acinetobacter* spp. (n=21). KPI-10 was the most potent agent with a MIC$_{90}$ value of 1 µg/ml; 14/21 (66.7%) of the isolates were resistant to currently available fluoroquinolones. KPI-10 activity was greater than eight-fold more potent than the other fluoroquinolones and all other agents except for tigecycline which had a MIC$_{90}$ value of 2 µg/ml.
- Gram-positive bacteria
  - *Enterococcus* spp. (n=72).
    - For *E. faecalis,* KPI-10 was two-fold more potent than ciprofloxacin and levofloxacin, equal in potency to gatifloxacin, and two-fold less potent than moxifloxacin based on the MIC$_{50}$ value. KPI-10 was at least four-fold more active than the other fluoroquinolones (MIC$_{90}$). Linezolid and vancomycin were the most potent agents with MIC$_{90}$ values of 2 µg/ml. KPI-10 was the next most potent agent with a MIC$_{90}$ value of 4 µg/ml.
    - All five fluoroquinolones had poor activity against *E. faecium* (n=24) with MIC$_{50/90}$ values that were greater than the highest concentration of antimicrobial tested.
  - β-hemolytic streptococci (n=55*).* The β-lactams cefepime, piperacillin-tazobactam and meropenem all had MIC$_{90}$ values at ≤0.5 µg/ml. KPI-10 was among the most potent agents with a MIC$_{90}$ value at 0.06 µg/ml. It was four-fold more potent than moxifloxacin, eight-fold more potent than gatifloxacin, and 16-fold more potent than ciprofloxacin and levofloxacin.
  - *Staphylococcus saprophyticus* (n=33). KPI-10 was the most potent agent with a MIC$_{90}$ value at 0.03 µg/ml, which was eight-fold more potent than moxifloxacin and gatifloxacin and 16-fold more potent than ciprofloxacin and levofloxacin.

Table 1. MIC frequency and cumulative percent inhibited distributions of KPI-10 and comparator fluoroquinolone antimicrobials.

Organism/ antimicrobial agent (no. tested)	No. (cumulative %) of isolates inhibited at antimicrobial MIC (µg/ml):														
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	MIC$_{50}$	MIC$_{90}$
E. coli (164)															
KPI-10	-[a]	4 (2.4)	73 (47.0)	27 (63.4)	5 (66.5)	6 (70.1)	2 (71.3)	7 (75.6)	19 (87.2)	14 (95.7)	7 (100.0)	-	-	0.03	2
Ciprofloxacin	2 (1.2)	49 (31.1)	54 (64.0)	3 (65.9)	0 (65.9)	4 (68.3)	3 (70.1)	2 (71.3)	1 (72.0)	0 (72.0)	3 (73.8)	2 (75.0)	41 (100.0)	0.015	>8
Levofloxacin	-	-	14 (8.5)	82 (58.5)	12 (65.9)	0 (65.9)	3 (67.7)	5 (70.7)	1 (71.3)	1 (72.0)	3 (73.8)	14 (82.3)	29 (100.0)	0.03	>8
Moxifloxacin	4 (2.4)	0 (2.4)	1 (3.1)	47 (31.7)	51 (62.8)	4 (65.2)	3 (67.1)	6 (70.7)	2 (72.0)	0 (72.0)	0 (72.0)	4 (74.4)	42 (100.0)	0.06	>8
Gatifloxacin	NT[b]	NT	NT	NT	106 (64.6)	2 (65.9)	2 (67.1)	7 (71.3)	0 (71.3)	1 (72.0)	5 (75.0)	26 (90.9)	15 (100.0)	≤0.06	8
Klebsiella spp. (54)															
KPI-10	-	-	1 (1.9)	6 (13.0)	24 (57.4)	4 (64.8)	2 (68.5)	3 (74.1)	3 (79.6)	1 (81.5)	2 (85.2)	1 (87.0)	7 (100.0)	0.06	>8
Ciprofloxacin	-	3 (5.6)	15 (33.3)	12 (55.6)	4 (63.0)	1 (64.8)	1 (66.7)	2 (70.4)	4 (77.8)	1 (79.6)	1 (81.5)	1 (83.3)	9 (100.0)	0.03	>8
Levofloxacin	-	-	1 (1.9)	9 (18.5)	22 (59.3)	2 (63.0)	0 (63.0)	3 (68.5)	5 (77.8)	0 (77.8)	2 (81.5)	3 (87.0)	7 (100.0)	0.06	>8
Moxifloxacin	-	-	-	2 (3.7)	14 (29.6)	16 (59.3)	2 (63.0)	1 (64.8)	5 (74.1)	1 (75.9)	3 (81.5)	1 (83.3)	9 (100.0)	0.12	>8
Gatifloxacin	NT	NT	NT	NT	30 (55.6)	4 (63.0)	1 (64.8)	3 (70.4)	3 (75.9)	3 (81.5)	1 (83.3)	5 (92.6)	4 (100.0)	≤0.06	8
Enterobacter spp. (51)															
KPI-10	-	-	1 (2.0)	8 (17.7)	24 (64.7)	10 (84.3)	2 (88.2)	3 (94.1)	0 (94.1)	1 (96.1)	1 (98.0)	1 (100.0)	-	0.06	0.5
Ciprofloxacin	-	10 (19.6)	25 (68.6)	6 (80.4)	3 (86.3)	1 (88.2)	1 (90.2)	3 (96.1)	0 (96.1)	2 (100.0)	-	-	-	0.015	0.25
Levofloxacin	-	-	1 (2.0)	21 (43.1)	19 (80.4)	1 (82.4)	2 (86.3)	2 (90.2)	3 (96.1)	1 (98.0)	1 (100.0)	-	-	0.06	0.5
Moxifloxacin	-	-	-	2 (3.9)	25 (52.9)	15 (82.4)	2 (86.3)	1 (88.2)	3 (94.1)	2 (98.0)	1 (100.0)	-	-	0.06	1
Gatifloxacin	NT	NT	NT	NT	37 (72.6)	5 (82.4)	2 (86.3)	3 (92.2)	2 (96.1)	1 (98.0)	1 (100.0)	-	-	≤0.06	0.5
Citrobacter spp. (34)															
KPI-10	-	-	8 (23.5)	4 (35.3)	12 (70.6)	1 (73.5)	2 (79.4)	0 (79.4)	4 (91.2)	0 (91.2)	1 (94.1)	0 (94.1)	2 (100.0)	0.06	1
Ciprofloxacin	1 (2.9)	15 (47.1)	8 (70.6)	2 (76.5)	1 (79.4)	1 (82.4)	0 (82.4)	1 (85.3)	2 (91.2)	0 (91.2)	0 (91.2)	2 (97.1)	1 (100.0)	0.015	1
Levofloxacin	-	-	2 (5.9)	15 (50.0)	8 (73.5)	1 (76.5)	1 (79.4)	0 (79.4)	2 (85.3)	2 (91.2)	0 (91.2)	1 (94.1)	2 (100.0)	0.03	2
Moxifloxacin	-	-	-	7 (20.6)	9 (47.1)	8 (70.6)	2 (76.5)	0 (76.5)	2 (82.4)	3 (91.2)	0 (91.2)	1 (94.1)	2 (100.0)	0.12	2
Gatifloxacin	NT	NT	NT	NT	24 (70.6)	2 (76.5)	0 (76.5)	2 (82.4)	2 (88.2)	1 (91.2)	1 (94.1)	0 (94.1)	2 (100.0)	≤0.06	2
P. mirabilis (43)															
KPI-10	-	-	-	2 (4.7)	14 (37.2)	13 (67.4)	0 (67.4)	3 (74.4)	1 (76.7)	3 (83.7)	3 (90.7)	3 (97.7)	1 (100.0)	0.12	4
Ciprofloxacin	-	1 (2.3)	19 (46.5)	9 (67.4)	0 (67.4)	1 (69.8)	0 (69.8)	0 (69.8)	2 (74.4)	3 (81.4)	1 (83.4)	3 (90.7)	4 (100.0)	0.12	8
Levofloxacin	-	-	1 (2.3)	5 (14.0)	20 (60.5)	3 (67.4)	0 (67.4)	1 (69.8)	0 (69.8)	4 (79.1)	3 (86.1)	1 (88.4)	5 (100.0)	0.06	>8
Moxifloxacin	-	-	-	-	-	3 (7.0)	9 (27.9)	17 (67.4)	0 (67.4)	1 (69.8)	0 (69.8)	3 (76.7)	10 (100.0)	0.5	>8
Gatifloxacin	NT	NT	NT	NT	2 (4.7)	22 (55.8)	5 (67.4)	0 (67.4)	1 (69.8)	1 (72.1)	3 (79.1)	2 (83.7)	7 (100.0)	0.12	>8
Indole-postive *Proteae* (44)															
KPI-10	-	-	-	-	2 (4.6)	11 (29.6)	9 (50.0)	2 (54.6)	2 (59.1)	6 (72.7)	6 (86.4)	5 (97.7)	1 (100.0)	0.25	8
Ciprofloxacin	1 (2.3)	8 (20.5)	9 (40.9)	1 (43.2)	1 (45.5)	0 (45.5)	0 (45.5)	4 (54.6)	3 (61.4)	1 (63.6)	2 (68.2)	6 (81.8)	8 (100.0)	0.5	>8
Levofloxacin	-	-	2 (4.6)	10 (27.3)	4 (36.4)	3 (43.2)	1 (45.5)	1 (47.7)	3 (54.6)	3 (61.4)	4 (70.5)	4 (79.6)	9 (100.0)	1	>8
Moxifloxacin	-	-	-	-	2 (4.6)	5 (15.9)	7 (31.8)	7 (47.7)	0 (47.7)	2 (52.3)	1 (54.6)	5 (65.9)	15 (100.0)	2	>8
Gatifloxacin	NT	NT	NT	NT	9 (20.5)	9 (40.9)	2 (45.5)	1 (47.7)	3 (54.6)	3 (61.4)	2 (65.9)	2 (70.5)	13 (100.0)	1	>8
P. aeruginosa (43)															
KPI-10	-	-	-	1 (2.3)	1 (4.7)	4 (14.0)	14 (46.5)	7 (62.8)	0 (62.8)	6 (76.7)	2 (81.4)	3 (88.4)	5 (100.0)	0.5	>8
Ciprofloxacin	-	-	-	1 (2.3)	8 (20.9)	16 (58.1)	1 (60.5)	2 (65.1)	1 (67.4)	5 (79.1)	1 (81.4)	2 (86.1)	6 (100.0)	0.12	>8
Levofloxacin	-	-	-	-	1 (2.3)	1 (4.7)	7 (20.9)	13 (51.2)	4 (60.5)	3 (67.4)	3 (74.4)	3 (81.4)	8 (100.0)	0.5	>8
Moxifloxacin	-	-	-	-	1 (2.3)	0 (2.3)	1 (4.7)	3 (11.6)	13 (41.9)	7 (58.1)	2 (62.8)	5 (74.4)	11 (100.0)	2	>8
Gatifloxacin	NT	NT	NT	NT	1 (2.3)	1 (4.7)	3 (11.6)	17 (51.2)	4 (60.5)	1 (62.8)	4 (72.1)	4 (81.4)	8 (100.0)	0.5	>8
WT-*Acinetobacter* spp. (21)															
KPI-10	-	-	4 (19.1)	2 (28.6)	1 (33.3)	0 (33.3)	2 (42.9)	5 (66.7)	5 90.5)	1 (95.2)	1 (100.0)	-	-	0.5	1
Ciprofloxacin	-	-	-	-	-	3 (14.3)	3 (28.6)	0 (28.6)	1 (33.3)	0 (33.3)	0 (33.3)	0 (33.3)	14 (100.0)	>8	>8
Levofloxacin	-	-	-	-	2 (9.5)	3 (23.8)	2 (33.3)	0 (33.3)	0 (33.3)	0 (33.3)	2 (42.9)	5 (66.7)	7 (100.0)	8	>8
Moxifloxacin	-	-	-	1 (4.8)	4 (23.8)	1 (28.6)	1 (33.3)	0 (33.3)	0 (33.3)	0 (33.3)	1 (38.1)	5 (61.9)	8 (100.0)	8	>8
Gatifloxacin	NT	NT	NT	NT	2 (9.5)	4 (28.6)	1 (33.3)	0 (33.3)	0 (33.3)	0 (33.3)	3 (47.6)	4 (66.7)	7 (100.0)	8	>8
Enterococcus spp. (72)															
KPI-10	-	-	-	-	-	-	12 (16.7)	25 (51.4)	1 (52.8)	5 (59.7)	3 (63.9)	7 (73.6)	19 (100.0)	0.5	>8
Ciprofloxacin	-	-	-	-	-	-	-	8 (11.1)	28 (50.0)	1 (51.4)	1 (52.8)	0 (52.8)	34 (100.0)	1	>8
Levofloxacin	-	-	-	-	-	-	-	2 (2.8)	32 (47.2)	3 (51.4)	1 (52.8)	0 (52.8)	34 (100.0)	2	>8
Moxifloxacin	-	-	-	-	-	1 (1.4)	30 (43.1)	4 (48.6)	2 (51.4)	1 (52.8)	1 (54.2)	5 (61.1)	28 (100.0)	1	>8
Gatifloxacin	NT	NT	NT	NT											
E. faecalis (45)															
KPI-10	-	-	-	-	-	-	10 (22.2)	24 (75.6)	1 (77.8)	5 (88.9)	3 (95.6)	2 (100.0)	-	0.5	4
Ciprofloxacin	-	-	-	-	-	-	-	7 (15.6)	26 (73.3)	1 (75.6)	0 (75.6)	0 (75.6)	11 (100.0)	1	>8
Levofloxacin	-	-	-	-	-	-	-	2 (4.4)	30 (71.1)	2 (75.6)	0 (75.6)	0 (75.6)	11 (100.0)	1	>8
Moxifloxacin	-	-	-	-	-	1 (2.2)	27 (62.2)	4 (71.1)	2 (75.6)	0 (75.6)	0 (75.6)	2 (80.0)	9 (100.0)	0.25	>8
Gatifloxacin	-	-	-	-	-	-	11 (24.4)	21 (71.1)	2 (75.6)	0 (75.6)	0 (75.6)	4 (84.4))	7 (100.0)	0.5	>8
E. faecium (24)															
KPI-10	-	-	-	-	-	-	-	-	-	-	-	5 (20.8)	19 (100.0)	>8	>8
Ciprofloxacin	-	-	-	-	-	-	-	-	-	-	1 (4.2)	0 (4.2)	23 (100.0)	>8	>8
Levofloxacin	-	-	-	-	-	-	-	-	-	-	1 (4.2)	0 (4.2)	23 (100.0)	>8	>8
Moxifloxacin	-	-	-	-	-	-	-	-	-	1 (4.2)	1 (8.3)	3 (20.8)	19 (100.0)	>8	>8
Gatifloxacin	-	-	-	-	-	-	-	-	-	1 (4.2)	0 (4.2)	1 (8.3)	22 (100.0)	>8	>8
β-haemolytic streptococci (55)															
KPI-10	-	-	1 (1.8)	20 (38.2)	34 (100.0)	-	-	-	-	-	-	-	-	0.06	0.06
Ciprofloxacin	-	-	-	-	-	-	4 (7.3)	39 (78.2)	7 (90.9)	5 (100.0)	-	-	-	0.5	1
Levofloxacin	-	-	-	-	-	-	1 (1.8)	33 (61.8)	16 (90.9)	5 (100.0)	-	-	-	0.5	1
Moxifloxacin	-	-	-	-	3 (5.5)	35 (69.1)	14 (94.6)	3 (100.0)	-	-	-	-	-	0.12	0.25
Gatifloxacin	NT	NT	NT	NT	-	4 (7.3)	43 (85.5)	8 (100.0)	-	-	-	-	-	0.25	0.5
S. saprophyticus (33)															
KPI-10	-	-	1 (3.0)	30 (93.9)	2 (100.0)	-	-	-	-	-	-	-	-	0.03	0.03
Ciprofloxacin	-	-	-	-	-	-	27 (81.8)	5 (97.0)	1 (100.0)	-	-	-	-	0.5	0.5
Levofloxacin	-	-	-	-	-	-	1 (3.0)	32 (100.0)	-	-	-	-	-	0.5	0.5
Moxifloxacin	-	-	-	-	-	28 (84.9)	5 (100.0)	-	-	-	-	-	-	0.12	0.25
Gatifloxacin	NT	NT	NT	NT	-	2 (6.1)	30 (97.0)	1 (100.0)	-	-	-	-	-	0.25	0.5

a. A dash indicates that no values were observed at that MIC value.
b. NT = dilution was not tested.

Table 2. Activity of KPI-10 and comparator antimicrobial agents tested against select groups of Gram-negative bacterial pathogens from North America and Europe.

Organism/antimicrobial agent/ (no. tested)	MIC (µg/ml)			CLSI[a]	EUCAST[a]
	MIC$_{50}$	MIC$_{90}$	Range	%S / %R	%S / %R
E. coli (164)					
KPI-10	0.03	2	0.008 – 4	- / -	- / -
Ciprofloxacin	0.015	>8	≤0.004 – >8	72.0 / 28.0	71.3 / 28.0
Levofloxacin	0.03	>8	0.015 – >8	72.0 / 26.2	71.3 / 28.0
Moxifloxacin	0.06	>8	≤0.004 – >8	- / -	70.7 / 28.0
Gatifloxacin	≤0.06	8	≤0.06 – >8	72.0 / 25.0	- / -
Ceftazidime	≤0.25	8	≤0.25 – >16	89.6 / 7.3	87.8 / 10.4
Cefepime	≤0.12	16	≤0.12 – >16	89.6 / 7.3	87.8 / 11.0
Meropenem	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	1	4	≤0.5 – >64	99.4 / 0.6	96.3 / 0.6
Amikacin	2	4	1 – 16	100.0 / 0.0	98.8 / 0.0
Tigecycline[b]	0.06	0.25	0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Klebsiella spp. (54)					
KPI-10	0.06	>8	0.015 – >8	- / -	- / -
Ciprofloxacin	0.03	>8	0.008 – >8	77.8 / 20.4	70.4 / 22.2
Levofloxacin	0.06	>8	0.015 – >8	77.8 / 18.5	77.8 / 22.2
Moxifloxacin	0.12	>8	0.03 – >8	- / -	64.8 / 25.9
Gatifloxacin	≤0.06	8	≤0.06 – >8	81.5 / 16.7	- / -
Ceftazidime	≤0.25	>16	≤0.25 – >16	77.8 / 16.7	75.9 / 22.2
Cefepime	≤0.12	>16	≤0.12 – >16	83.3 / 11.1	81.5 / 16.7
Meropenem	≤0.06	≤0.06	≤0.06 – 2	98.1 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	>64	≤0.5 – >64	87.0 / 11.1	83.3 / 13.0
Amikacin	1	2	≤0.5 – >64	98.1 / 1.9	94.4 / 1.9
Tigecycline[b]	0.25	0.5	0.06 – 4	98.1 / 0.0	96.3 / 1.9
Enterobacter spp.[c] (51)					
KPI-10	0.06	0.5	0.015 – 8	- / -	- / -
Ciprofloxacin	0.015	0.25	0.008 – 2	96.1 / 0.0	96.1 / 3.9
Levofloxacin	0.06	0.5	0.015 – 4	98.0 / 0.0	96.1 / 2.0
Moxifloxacin	0.06	1	0.03 – 4	- / -	88.2 / 5.9
Gatifloxacin	≤0.06	0.5	≤0.06 – 4	98.0 / 0.0	- / -
Ceftazidime	0.5	>16	≤0.25 – >16	76.5 / 23.5	74.5 / 23.5
Cefepime	≤0.12	4	≤0.12 – >16	94.1 / 5.9	86.3 / 7.8
Meropenem	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	64	≤0.5 – >64	84.3 / 5.9	82.4 / 15.7
Amikacin	1	2	≤0.5 – >64	96.1 / 2.0	96.1 / 3.9
Tigecycline[b]	0.25	0.5	0.06 – 2	100.0 / 0.0	96.1 / 0.0
P. mirabilis (43)					
KPI-10	0.12	4	0.03 – >8	- / -	- / -
Ciprofloxacin	0.03	8	0.008 – >8	74.4 / 18.6	69.8 / 25.6
Levofloxacin	0.06	>8	0.015 – >8	79.1 / 14.0	69.8 / 20.9
Moxifloxacin	0.5	>8	0.12 – >8	- / -	67.4 / 32.6
Gatifloxacin	0.12	>8	≤0.06 – >8	72.1 / 20.9	- / -
Ceftazidime	≤0.25	≤0.25	≤0.25 – 2	100.0 / 0.0	97.7 / 0.0
Cefepime	≤0.12	0.25	≤0.12 – >16	97.7 / 2.3	97.7 / 2.3
Meropenem	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Amikacin	4	4	2 – 64	97.7 / 2.3	97.7 / 2.3
Tigecycline[b]	1	2	0.25 – >4	93.0 / 2.3	53.5 / 7.0
P. aeruginosa (43)					
KPI-10	0.5	8	0.12 – >8	- / -	- / -
Ciprofloxacin	0.12	8	0.06 – >8	68.2 / 18.2	63.6 / 31.8
Levofloxacin	0.5	>8	0.25 – >8	68.2 / 18.2	63.6 / 31.8
Moxifloxacin	2	>8	0.5 – >8	- / -	- / -
Gatifloxacin	0.5	>8	0.25 – >8	63.6 / 22.7	- / -
Ceftazidime	2	>16	1 – >16	81.8 / 18.2	81.8 / 18.2
Cefepime	2	16	0.5 – 16	86.4 / 0.0	86.4 / 13.6
Meropenem	0.5	4	0.12 – 4	100.0 / 0.0	81.8 / 0.0
Piperacillin/tazobactam	4	>64	1 – >64	81.8 / 18.2	81.8 / 18.2
Amikacin	4	8	1 – 16	100.0 / 0.0	90.9 / 0.0
Tigecycline[b]	4	>4	1 – >4	- / -	- / -
Acinetobacter spp.[d] (wild-type, 21)					
KPI-10	0.5	1	0.015 – 4	- / -	- / -
Ciprofloxacin	>8	>8	0.12 – >8	33.3 / 66.7	33.3 / 66.7
Levofloxacin	8	>8	0.06 – >8	33.3 / 57.1	33.3 / 66.7
Moxifloxacin	8	>8	0.03 – >8	- / -	- / -
Gatifloxacin	8	>8	≤0.06 – >8	33.3 / 52.4	- / -
Ceftazidime	16	>16	1 – >16	42.9 / 47.6	- / -
Cefepime	>16	>16	1 – >16	47.6 / 52.4	- / -
Meropenem	>8	>8	0.12 – >8	47.6 / 52.4	47.6 / 52.4
Piperacillin/tazobactam	>64	>64	≤0.5 – >64	42.9 / 57.1	- / -
Amikacin	4	>64	≤0.5 – >64	61.9 / 38.1	61.9 / 38.1
Tigecycline[b]	1	2	0.06 – 4	- / -	- / -

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. USA-FDA breakpoints were applied [Tygacil Product Insert, 2012].
c. Includes: *Enterobacter aerogenes* (15 strains), *E. cloacae* (35 strains), and *E. intermedius* (1 strain).
d. Includes: *Acinetobacter baumannii* (18 strains), *A. lwoffii* (1 strain), and unspeciated *Acinetobacter* (2 strains).

Table 3. Activity of KPI-10 and comparator antimicrobial agents tested against select groups of Gram-positive bacterial pathogens from North America and Europe.

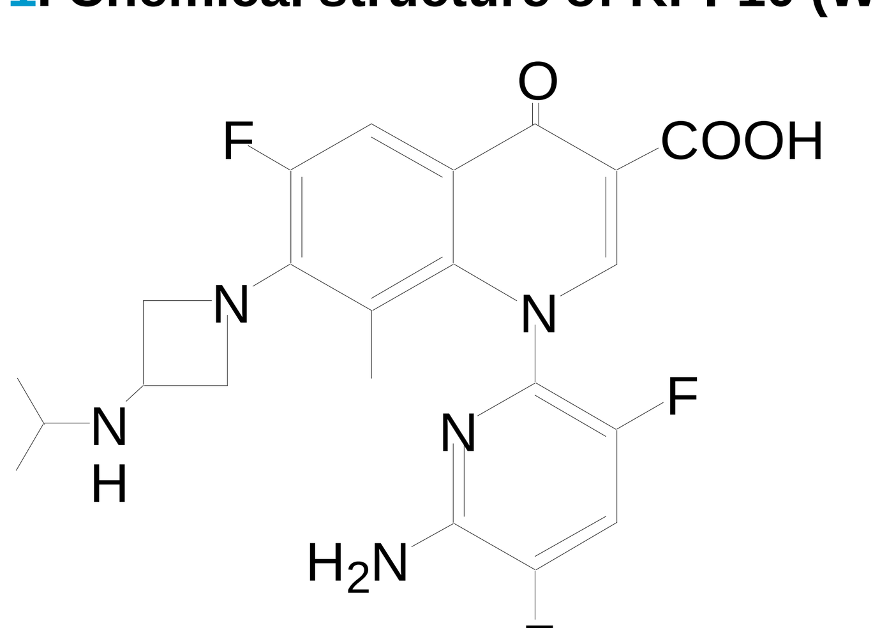
Organism/ agent (no. tested)	MIC$_{50}$	MIC$_{90}$	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Enterococcus spp.[b] (72)					
KPI-10	0.5	>8	0.25 – >8	- / -	- / -
Ciprofloxacin	1	>8	0.5 – >8	50.0 / 48.6	- / -
Levofloxacin	2	>8	0.5 – >8	51.4 / 47.2	- / -
Moxifloxacin	1	>8	0.12 – >8	- / -	- / -
Gatifloxacin	1	>8	0.25 – >8	52.8 / 47.2	- / -
Erythromycin	>4	>4	≤0.25 – >4	8.3 / 61.1	- / -
Clindamycin	>2	>2	≤0.25 – >2	- / -	- / -
Pip/Taz[c]	4	>64	1 – >64	68.1 / -	68.1 / -
Amikacin	>64	>64	16 – >64	- / -	- / -
Linezolid	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	>16	0.5 – >16	77.8 / 22.2	77.8 / 22.2

Organism/ agent (no. tested)	MIC$_{50}$	MIC$_{90}$	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
β-haemolytic streptococci[d] (55)					
KPI-10	0.06	0.06	0.015 – 0.06	- / -	- / -
Ciprofloxacin	0.5	1	0.25 – 2	- / -	- / -
Levofloxacin	0.5	1	0.25 – 2	100.0 / 0.0	90.9 / 0.0
Moxifloxacin	0.12	0.25	0.06 – 0.5	- / -	100.0 / 0.0
Gatifloxacin	0.25	0.5	0.12 – 0.5	100.0 / 0.0	- / -
Erythromycin	≤0.25	>4	≤0.25 – >4	74.5 / 25.5	74.5 / 25.5
Clindamycin	≤0.25	>2	≤0.25 – >2	81.8 / 18.2	81.8 / 18.2
Cefepime	≤0.12	≤0.12	≤0.12 – 1	98.2 / -	100.0 / 0.0
Meropenem	≤0.06	≤0.06	≤0.06 – 0.25	100.0 / -	100.0 / 0.0
Pip/Taz[c]	≤0.5	≤0.5	≤0.5	- / -	100.0 / 0.0
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0

Organism/ agent (no. tested)	MIC$_{50}$	MIC$_{90}$	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
S. saprophyticus (33)					
KPI-10	0.03	0.03	0.015 – 0.06	- / -	- / -
Ciprofloxacin	0.25	0.5	0.25 – 1	100.0 / 0.0	100.0 / 0.0
Levofloxacin	0.5	0.5	0.25 – 0.5	100.0 / 0.0	100.0 / 0.0
Moxifloxacin	0.12	0.25	0.12 – 0.25	100.0 / 0.0	100.0 / 0.0
Gatifloxacin	0.25	0.25	0.12 – 0.5	100.0 / 0.0	- / -
Erythromycin	≤0.25	>2	≤0.25 – >2	54.5 / 45.5	54.5 / 45.5
Clindamycin	≤0.25	>2	≤0.25 – >2	81.8 / 18.2	81.8 / 18.2
Ceftazidime	16	16	8 – >16	9.1 / 9.1	- / -
Cefepime	2	2	0.5 – 4	100.0 / 0.0	- / -
Meropenem	0.25	0.25	0.12 – 0.5	100.0 / 0.0	- / -
Pip/Taz[c]	1	2	≤0.5 – 2	100.0 / 0.0	- / -
Amikacin	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. Includes: *Enterococcus casseliflavus* (1 strain), *E. faecalis* (45 strains), *E. faecium* (24 strains), and *E. gallinarum* (2 strains).
c. Piperacillin/tazobactam.
d. Includes: Group A *Streptococcus* (8 strains), Group B *Streptococcus* (45 strains), and Group G *Streptococcus* (2 strains).

Figure 1. Chemical structure of KPI-10 (WQ-3810)



Conclusions

- KPI-10 was the most active fluoroquinolone tested against Gram-positive organism groups and among the most active for Gram-negative organisms.
- KPI-10 exhibited a potent broad spectrum of activity including activity against select Gram-positive and -negative bacteria resistant to the currently available fluoroquinolones.
- The data suggest that KPI-10 merits clinical evaluation for use in UTI, including UTI due to emerging fluoroquinolone-resistant *E. coli.*

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