F-2053

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* (MIC₉₀ for all *E. coli*, 2 µg/ml). However, based on MIC₅₀ 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 $(MIC_{90}, 1 \mu g/ml)$ was more than eight-fold greater than that of other FQ. The KPI-10 MIC₉₀ 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* (MIC₅₀ 0.5 versus 0.12 µg/ml). It was two- to eight-fold more potent, and four- to 16fold 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 MIC₅₀ value, but at least four-fold more active than other fluoroquinolones using the MIC_{qq} 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.

- pathogens are presented in Tables 2 and 3, respectively.
- Gram-negative bacteria
- o Enterobacteriaceae
- µg/ml.
- µg/ml
- Non-fermenters
- levofloxacin and gatifloxacin was 0.5 µg/ml.
- tigecycline which had a MIC_{90} value of 2 µg/ml.
- Gram-positive bacteria
- Enterococcus spp. (n=72).
- MIC_{90} value of 4 µg/ml.
- greater than the highest concentration of antimicrobial tested.
- fold more potent than ciprofloxacin and levofloxacin.
- than ciprofloxacin and levofloxacin.

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

R.K. FLAMM, D.J. BIEDENBACH, H.S. SADER, M.L. KONRARDY, R.N. JONES JMI Laboratories, North Liberty, Iowa, USA

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

Escherichia coli (n=164). Tigecycline was the most potent agent against E. coli with a MIC₉₀ value at 0.25 μ g/ml for all isolates. KPI-10 exhibited a MIC₉₀ value at 2 μ g/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 μ g/ml while for ciprofloxacin the MIC_{50/90} value was >8/>8 μ g/ml.

Enterobacter spp. (n=51). Ciprofloxacin was the most potent agent with a MIC₉₀ value of 0.25 µg/ml for all isolates. KPI-10, levofloxacin, gatifloxacin, and tigecycline demonstrated MIC₉₀ values at 0.5

Klebsiella spp. (n=54). Tigecycline and amikacin were the most potent agents with MIC₉₀ values of 0.5 and 2 μ g/ml, respectively. The MIC₉₀ values for the fluoroquinolones ranged from 8 μ g/ml for gatifloxacin to $>8 \mu g/ml$ 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 MIC₉₀ values of $\leq 0.5 \,\mu$ g/ml. KPI-10 was the most potent fluoroguinolone with a MIC₉₀ value of 4 μ g/ml. The other fluoroguinolones had MIC₉₀ values at 8->8

■ Pseudomonas aeruginosa (n=43). Meropenem was the most potent agent with a MIC₉₀ value of 4 μ g/ml. The MIC₉₀ values for KPI-10 and the other fluoroguinolones including ciprofloxacin and levofloxacin were >8 μ g/ml. The MIC₅₀ value for ciprofloxacin was 0.12 μ g/ml and for KPI-10,

• Acinetobacter spp. (n=21). KPI-10 was the most potent agent with a MIC₄₀ value of 1 μ g/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

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 MIC₅₀ 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 MIC₉₀ values of 2 μ g/ml. KPI-10 was the next most potent agent with a

• All five fluoroquinolones had poor activity against *E. faecium* (n=24) with MIC_{50/90} values that were

 \circ β -hemolytic streptococci (n=55). The β -lactams cefepime, piperacillin-tazobactam and meropenem all had MIC₉₀ values at $\leq 0.5 \mu g/ml$. KPI-10 was among the most potent agents with a MIC₉₀ value at 0.06 µg/ml. It was four-fold more potent than moxifloxacin, eight-fold more potent than gatifloxacin, and 16-

• Staphylococcus saprophyticus (n=33). KPI-10 was the most potent agent with a MIC₉₀ value at 0.03 µg/ml, which was eight-fold more potent than moxifloxacin and gatifloxacin and 16-fold more potent

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

Understand Underst				lobia												
norm from tensers) 93.004 0.008 0.01 0.03 0.02 0.2 0.2 1 2 4 8 >80 MCc,	Organism/ antimicrobial				No. (cu	nulative %	b) of isola	tes inhibit	ed at antin	nicrobial	MIC (µg/m	nl):				
C offelt A (2,4) 744/10 21/13 71/10	agent (no. tested)	≤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
GP:10 - <td><i>E. coli</i> (164)</td> <td></td>	<i>E. coli</i> (164)															
Landbacen (J. 1997) (J. 1998) (J. 1997) (J. 1998) (J. 1998) (J. 1997) (J. 1998) (J. 19	KPI-10 Ciproflovacin	_a 2 (1 2)	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)	- 2 (75 0)	- 41 (100 0)	0.03	2
Solutionscin (1,2) (0,2,0) (0,3)	Levofloxacin	2 (1.2) -	49 (31.1)	54 (64.0) 14 (8.5)	3 (65.9)	0 (65.9) 12 (65.9)	4 (68.3) 0 (65.9)	3 (70.1)	2(71.3) 5(70.7)	1 (72.0)	0 (72.0) 1 (72.0)	3 (73.8)	2 (75.0) 14 (82.3)	41 (100.0) 29 (100.0)	0.015	>8 >8
$ \begin{array}{c} \text{Cattloscen} & N^{N} & N & N & N & N & N & N & N & N & N & N & O &$	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
Additional of the state of the sta	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
CippelDocach	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
Levoltancen Levolt	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
Madificacin . . 2 2 7 4 2 1 6 1 7 1 <th< td=""><td>Levofloxacin</td><td>-</td><td>-</td><td>1 (1.9)</td><td>9 (18.5)</td><td>22 (59.3)</td><td>2 (63.0)</td><td>0 (63.0)</td><td>3 (68.5)</td><td>5 (77.8)</td><td>0 (77.8)</td><td>2 (81.5)</td><td>3 (87.0)</td><td>7 (100.0)</td><td>0.06</td><td>>8</td></th<>	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
Cardinalization program CPI-10 CI N	Moxifloxacin	- NIT	- NIT	- NT	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
priprior ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< ·< <	Enterobacter spp. (51)	IN I	IN I	IN I	IN I	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
Capantinamin - - - - - - - - 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.05 0.016 0.016 0.016 0.016 0.016 0.016 0.05 0.016 0.02 0.012 0.012 0.011 0.012 0.011 0.011 0.016 0.016 0.012	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
Lardenbargen 1 12.0 21 (3.1) 19 (20) 19 (2.1) 29 (3.1) 19 (2.1) 29 (3.1) 19 (2.1) 19 (3.0) 11 (10.0) 0.08 0.5 (3.10) 0.6	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
Cardiocarian NT	Levofloxacin	-	-	1 (2.0)	21 (43.1)	19 (80.4) 25 (52.0)	1 (82.4)	2 (86.3)	2 (90.2)	3 (96.1)	1 (98.0)	1 (100.0)	-	-	0.06	0.5
Cambaersp. (34) KPI-10	Gatifloxacin	- NT	- NT	- NT	2 (3.9) NT	25 (52.9) 37 (72.6)	5 (82.4)	2 (86.3)	3 (92.2)	3 (94.1) 2 (96.1)	2 (98.0) 1 (98.0)	1 (100.0)	-	-	0.06 ≤0.06	0.5
KRI-10 - - 8 (22.5) (47.5.5) (77.4.1) (97.2.5) (97.4.1) (97.2.5) (97.4.1) (97.2.5) (97.4.1) (97.2.5) (97.4.1) (97.4.5) (97.4.1)	Citrobacter spp. (34)						- ()	_()	- ()	_(,	()	. ()				
Leprentament 1, Ley 1, 15 (4^{-1}) 15 (4^{-1}) 16 (4^{-1}) 16 (4^{-1}) 16 (4^{-1}) 082-4 1 (4^{-1}) 0734 1	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
$ \begin{array}{c} \begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	Ciprofloxacin	1 (2.9)	15 (47.1)	8 (70.6) 2 (5 0)	2 (76.5) 15 (50.0)	1 (79.4) 8 (73.5)	1 (82.4) 1 (76.5)	U (82.4) 1 (70.4)	1 (85.3) 0 (70 4)	2 (91.2)	0 (91.2) 2 (01.2)	0 (91.2) 0 (91.2)	2 (97.1) 1 (04 1)	1 (100.0) 2 (100.0)	0.015	1 2
Cardinacian NT NT NT NT 22 (70.6) 2 (76.5) 2 (76.5) 2 (82.4) 2 (82.1) 1 (92.1) 4 (94.1) 0 (94.1) 2 (100.0) 30.02 2 KPI-10 - - - 2 (77.4) 1 (87.2) 1 (77.2) 1	Moxifloxacin	-	-	∠ (0.9) -	7 (20.6)	9 (47.1)	8 (70.6)	2 (76.5)	0 (76.5)	2 (82.4)	2 (91.2) 3 (91.2)	0 (91.2)	1 (94.1)	2 (100.0)	0.03	2
P. mitability (45) Vertion	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
nr-nu - - 2 (4,7) 1 (3/2) 13 (3/2) 13 (4/2) 1 (1/2,3) 13 (4/3) 12 (3/2) 13 (4/3) 12 (3/2) 13 (4/3) 12 (3/2) 13 (4/3) 12 (3/2) 13 (4/3) 12 (3/2) 13 (4/3)	P. mirabilis (43)				$o(4\pi)$	A A (07 C)	40 (07 1)		0/74	4 (70 -)	0 (00 T)		0 (07 =)	4 (400 0)	0.40	
$ \begin{array}{c} \mbox \mbo$	KPI-10 Ciproflovacin	-	- 1 (2 2)	- 19 (16 5)	2 (4.7) 9 (67 1)	14 (37.2) 0 (67 4)	13 (67.4) 1 (60 8)	U (67.4) 0 (60 8)	3 (74.4) 0 (60.8)	1 (76.7) 2 (74 4)	3 (83.7) 3 (81 4)	3 (90.7) 1 (83 4)	3 (97.7) 3 (97.7)	1 (100.0) 4 (100.0)	0.12 0.12	4 Ջ
Modificacian N <t< td=""><td>Levofloxacin</td><td>-</td><td>-</td><td>1 (2.3)</td><td>5 (14.0)</td><td>20 (60.5)</td><td>3 (67.4)</td><td>0 (03.0) 0 (67.4)</td><td>1 (69.8)</td><td>2 (74.4) 0 (69.8)</td><td>4 (79.1)</td><td>3 (86.1)</td><td>3 (90.7) 1 (88.4)</td><td>5 (100.0)</td><td>0.12</td><td>>8</td></t<>	Levofloxacin	-	-	1 (2.3)	5 (14.0)	20 (60.5)	3 (67.4)	0 (03.0) 0 (67.4)	1 (69.8)	2 (74.4) 0 (69.8)	4 (79.1)	3 (86.1)	3 (90.7) 1 (88.4)	5 (100.0)	0.12	>8
Gattioxacin NT NT NT NT 2 (4.7) 22 (58.) 5 (67.4) 0 (67.4) 1 (8.8) 1 (72.1) 3 (7.51) 2 (8.3.7) 7 (100.0) 0.12 >8 (PP-10 2 (4.6) 11 (29.6) 9 (50.0) 2 (54.6) 2 (59.1) 6 (72.7) 6 (8.6.4) 5 (97.7) 1 (100.0) 0.55 >8 (Pp-100 - 2 (4.6) 10 (27.3) 4 (4.6) 1 (42.5) 2 (45.5) 1 (45.7) 1 (45.7) 2 (82.3) (45.5) 1 (45.5) 1 (45.7) 2 (4.6) 10 (27.3) 4 (4.6) 1 (28.2) 6 (45.7) 2 (8.6) 1 (45.5) 1 (45.7) 2 (8.6) 1 (45.7) 2 (8.6) 1 (45.7) 2 (8.6) 1 (45.7) 1 (100.0) 0.5 >8 (Partioxacin NT NT NT NT NT 9 (20.5) 9 (40.9) 1 (45.5) 1 (47.7) 3 (45.4) 1 (45.7) 2 (26.3) 1 (47.7) 3 (45.6) 1 (45.7) 2 (8.6) 1 (47.7) 3 (45.6) 1 (45.7) 2 (8.6) 1 (47.7) 3 (45.6) 1 (45.7) 2 (8.6) 1 (45.7) 1 (45	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
Incode posible Projecte (14) FP-10 F2-10	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
CipcelDocacin 1 (2.3) B (20.5) 0 (40.9) 1 (45.5) 0 (46.5)	Indole-postive Proteae	- (44)	_	_	_	2 (4 6)	11 (29.6)	9 (50 0)	2 (54 6)	2 (50 1)	6 (72 7)	6 (86 4)	5 (97 7)	1 (100 0)	0.25	8
Levoltoxacin - 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 (70.0) 1 >> 8 Gatifloxacin NT NT NT NT NT 9 (20.5) 9 (40.9) 2 (45.5) 1 (47.7) 0 (47.7) 2 (52.3) 1 (54.6) 5 (56.9) 1 (510.0) 2 >> 8 Gatifloxacin 1 (2.3) 1 (4.7) 4 (14.0) 14 (45.5) 7 (62.8) 0 (67.6) 2 (81.4) 3 (88.4) 5 (100.0) 0.5 >> 8 Gatifloxacin 1 (2.3) 1 (4.7) 7 (20.9) 13 (51.4) 16 (62.8) 6 (76.7) 2 (81.4) 3 (88.4) 5 (100.0) 0.5 >> 8 Gatifloxacin 1 (2.3) 1 (4.7) 7 (20.9) 13 (51.2) 1 (62.8) 6 (74.7) 3 (74.4) 3 (81.4) 8 (100.0) 0.5 >> 8 Gatifloxacin 1 (2.3) 0 (2.3) 1 (4.7) 7 (20.9) 13 (51.2) (62.8) 6 (74.7) 3 (74.4) 3 (81.4) 8 (100.0) 0.5 >> 8 Gatifloxacin	Ciprofloxacin	1 (2.3)	8 (20.5)	9 (40.9)	1 (43.2)	1 (45.5)	0 (45.5)	9 (30.0) 0 (45.5)	2 (54.6) 4 (54.6)	2 (39.1) 3 (61.4)	1 (63.6)	2 (68.2)	6 (81.8)	8 (100.0)	0.25	>8
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Enterococcus spp. (72) KPI-10	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
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CiprofitoXatin -	KPI-10 Ciproflevenin	-	-	-	-	-	-	12 (16.7)	25 (51.4)	1 (52.8)	5 (59.7)	3 (63.9)	7 (73.6)	19 (100.0)	0.5	>8
Moxifloxacin I <t< td=""><td>Levofloxacin</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>o (11.1) 2 (2.8)</td><td>∠o (50.0) 32 (47 2)</td><td>1 (51.4) 3 (51.4)</td><td>1 (52.8) 1 (52.8)</td><td>0 (52.8) 0 (52.8)</td><td>34 (100.0) 34 (100.0)</td><td>ו 2</td><td>>ö >8<</td></t<>	Levofloxacin	-	-	-	-	-	-	-	o (11.1) 2 (2.8)	∠o (50.0) 32 (47 2)	1 (51.4) 3 (51.4)	1 (52.8) 1 (52.8)	0 (52.8) 0 (52.8)	34 (100.0) 34 (100.0)	ו 2	>ö >8<
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$\begin{array}{cccccccccccccccccccccccccccccccccccc$	E. taecalis (45)							10 (วว ว)	21 (75 G)	1 (77 0)	5 (89 0)	3 (05 6)	2 (100 0)	_	05	Л
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$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Gatifloxacin	-	-	-	-	-	-	11 (24.4)	21 (71.1)	2 (75.6)	U (75.6)	U (75.6)	4 (84.4))	7 (100.0)	0.5	>8
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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Levofloxacin	-	-	-	-	-	-	-	-	-	-	1 (4.2)	0 (4.2)	23 (100.0)	>8	>8
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Moxifloxacin	-	-	-	-	-	-	-	-	-	1 (4.2)	1 (8.3)	3 (20.8)	19 (100.0)	>8	>8
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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) - - - 0.5 1 Moxifloxacin NT NT NT NT - 4 (7.3) 43 (85.5) 8 (100.0) - - - 0.12 0.25 Gatifloxacin NT NT NT NT - 4 (7.3) 43 (85.5) 8 (100.0) - - - 0.025 0.5 S. saprophyticus (33) - - - - - - - - 0.03 0.03 Ciprofloxacin - - - - 27 (81.8) 5 (97.0) 1 (100.0) - - - 0.5 0.5 Levofloxacin -	KPI-10	-	-	1 (1.8)	20 (38.2)	34 (100.0)	-	-	-	-	-	-	-	-	0.06	0.06
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) - - - - 0.55 1 Gatifloxacin NT NT NT NT - 4 (7.3) 43 (85.5) 8 (100.0) - - - - 0.55 0.55 S. saprophyticus (33) - - - - - - - - 0.03 0.03 KPI-10 - - - - - - - - - 0.03 0.03 Ciprofloxacin - - - - - - - - - - 0.05 0.5 Levofloxacin - - - - - - 1 (3.0) 32 (100.0) - - - 0.5 0.5 Moxifloxacin - - - -	Ciprofloxacin	-	-	-	-	-	-	4 (7.3)	39 (78.2)	7 (90.9)	5 (100.0)	-	-	-	0.5	1
MOXINIXACIN - - - - - - - 0.12 0.25 Gatifloxacin NT NT NT NT NT - 4 (7.3) 43 (85.5) 8 (100.0) - - - - - 0.12 0.25 Gatifloxacin NT NT NT NT - 4 (7.3) 43 (85.5) 8 (100.0) - - - - - - 0.25 0.5 0.5 S. saprophyticus (33) KPI-10 - - 1 (3.0) 30 (93.9) 2 (100.0) - - - - - - 0.03 0.03 0.03 Ciprofloxacin - - - - - - - - - - 0.5 0.12 0.25	Levofloxacin	-	-	-	-	-	-	1 (1.8)	33 (61.8)	16 (90.9)	5 (100.0)	-	-	-	0.5	1
S. saprophyticus (33) KPI-10 - - 1 (3.0) 30 (93.9) 2 (100.0) - - - - - 0.03 0.03 Ciprofloxacin - - - - - - - - 0.03 0.03 Levofloxacin - - - - - - - 0.5 0.5 Moxifloxacin - - - - 1 (3.0) 32 (100.0) - - - 0.5 0.5 Moxifloxacin - - - - 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	MOXITIOXACIN Gatifloxacin	- NT	- NIT	- NT	- NIT	3 (5.5) -	35 (69.1) 4 (7 3)	14 (94.6) 43 (85 5)	ა (100.0) 8 (100 0)	-	-	-	-	-	0.12 0.25	0.25 0.5
KPI-10 - - 1 (3.0) 30 (93.9) 2 (100.0) - 0.03 0.05 0.5	S. saprophyticus (33)	IN Í	INI	INT	INI	-	ч (1.3)		0 (100.0)	-	-	-	-	-	0.20	0.0
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 - - - 1 (3.0) 32 (100.0) - - - - 0.5 0.5 Gatifloxacin NT NT NT NT 2 (6.1) 30 (97.0) 1 (100.0) - - - - 0.5 0.5 Gatifloxacin NT NT NT NT 2 (6.1) 30 (97.0) 1 (100.0) - - - - 0.12 0.25 0.5	KPI-10	-	-	1 (3.0)	30 (93.9)	2 (100.0)	-	-	-	-	-	-	-	-	0.03	0.03
Levonoxacin - - - - 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 - 2 (6.1) 30 (97.0) 1 (100.0) - - - 0.25 0.5	Ciprofloxacin	-	-	-	-	-	-	27 (81.8)	5 (97.0)	1 (100.0)	-	-	-	-	0.5	0.5
Gatifloxacin NT NT NT NT - 2 (6.1) 30 (97.0) 1 (100.0) - - - - 0.12 0.23 0.25 0.5 0.25 0.5 0.5 0.12 0.25 0.5	Levotioxacin Moxifloxacin	-	-	-	-	-	- 28 (84 9)	1 (3.0) 5 (100 0)	32 (100.0) -	-	-	-	-	-	0.5 0.12	0.5 0.25
	Gatifloxacin	NT	NT	NT	NT	-	<u>2</u> (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 3. Activity of KPI-10 and comparator antimicrobial agents tested against select groups of Gram-positive bacterial pathogens from North America and Europe.

Organism/	I	MIC (µg/ml)			ELIO A OTA	Organism/	MIC (µg/ml)					Organism/	MIC (µg/ml)				FUO ACT3
tested)	MIC ₅₀	MIC ₉₀	Range	°CLSIª %S / %R	%S/%R	agent (no. tested)	MIC ₅₀	MIC ₉₀	Range	°CLSIª %S / %R	%S/%R	tested)	MIC ₅₀	MIC ₉₀	Range	%S / %R	%S/%R
Enterococcus spp.	^b (72)					β-haemolytic strep	tococci ^d (55)					S. saprophyticus (33	3)				
KPI-10	0.5	>8	0.25 – >8	- / -	- / -	KPI-10	0.06	0.06	0.015 – 0.06	- / -	- / -	KPI-10	0.03	0.03	0.015 – 0.06	- / -	- / -
Ciprofloxacin	1	>8	0.5 ->8	50.0 / 48.6	- / -	Ciprofloxacin	0.5	1	0.25 – 2	- / -	- / -	Ciprofloxacin	0.25	0.5	0.25 – 1	100.0 / 0.0	100.0 / 0.0
Levofloxacin	2	>8	0.5 ->8	51.4 / 47.2	- / -	Levofloxacin	0.5	1	0.25 – 2	100.0 / 0.0	90.9 / 0.0	Levofloxacin	0.5	0.5	0.25 – 0.5	100.0 / 0.0	100.0 / 0.0
Moxifloxacin	1	>8	0.12 – >8	- / -	- / -	Moxifloxacin	0.12	0.25	0.06 - 0.5	- / -	100.0 / 0.0	Moxifloxacin	0.12	0.25	0.12 – 0.25	100.0 / 0.0	100.0 / 0.0
Gatifloxacin	1	>8	0.25 – >8	52.8 / 47.2	- / -	Gatifloxacin	0.25	0.5	0.12 – 0.5	100.0 / 0.0	- / -	Gatifloxacin	0.25	0.25	0.12 – 0.5	100.0 / 0.0	- / -
Erythromycin	>4	>4	≤0.25 – >4	8.3/61.1	- / -	Erythromycin	≤0.25	>4	≤0.25 – >4	74.5 / 25.5	74.5 / 25.5	Erythromycin	≤0.25	>2	≤0.25 – >2	54.5 / 45.5	54.5 / 45.5
Clindamycin	>2	>2	≤0.25 – >2	- / -	- / -	Clindamycin	≤0.25	>2	≤0.25 – >2	81.8 / 18.2	81.8 / 18.2	Clindamycin	≤0.25	>2	≤0.25 – >2	81.8/18.2	81.8 / 18.2
Pip/Taz ^c	4	>64	1 – >64	68.1 / -	68.1 / -	Cefepime	≤0.12	≤0.12	≤0.12 – 1	98.2 / -	100.0 / 0.0	Ceftazidime	16	16	8->16	9.1 / 9.1	- / -
Amikacin	>64	>64	16 – >64	- / -	- / -	Meropenem	≤0.06	≤0.06	≤0.06 – 0.25	100.0 / -	100.0 / 0.0	Cefepime	2	2	0.5 – 4	100.0 / 0.0	- / -
Linezolid	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0	Pip/Taz⁰	≤0.5	≤0.5	≤0.5	- / -	100.0 / 0.0	Meropenem	0.25	0.25	0.12 – 0.5	100.0 / 0.0	- / -
Vancomycin	1	>16	0.5 – >16	77.8 / 22.2	77.8/22.2	Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0	Pip/Taz⁰	1	2	≤0.5 – 2	100.0 / 0.0	- / -
						Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0	Amikacin	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
a Criteria as pub	ished by the C	I SI [2012] :	and FUCAST [2012]								Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
b. Includes: Enter		eliflavus (1 s	train). <i>E. faeca</i>	olis (45 strains). E	<i>faecium</i> (24 strai	ns), and <i>E. gallinarum</i> ((2 strains).					Vancomycin	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0

c. Piperacillin/tazobactam

d. Includes: Group A Streptococcus (8 strains), Group B Streptococcus (45 strains), and Group G Streptococcus (2 strains).

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

America and Europe.

Drganism/antimicrobial		MIC (µg	ı/ml)	CLSI ^a	EUCAST ^a
agent/ (no. tested)	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	-/- 720/250	/0.7/28.0
Ceftazidime	≤0.00 <0.25	ð 8	≤0.00 - >8 <0.25 - >16	72.0725.0	-/- 878/10/
Cefepime	<u></u> ≤0.23 ≤0.12	16	≤0.23 = >16	896/73	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
(lebsiella spp. (54)	0.00	•	0.045 0	,	,
KPI-10 Ciproflovacio	0.06	>8	0.015 - >8	-/- 77 9/20 4	- / -
Levefloxacin	0.03	>0	0.006 - >8	778/185	70.4/22.2
Moxifloxacin	0.00	>8	0.013 - >8	- / -	64 8 / 25 9
Gatifloxacin	<0.12	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	-/-	-/-
Cipronoxacin	0.015	0.25	0.008 - 2	96.1/0.0	96.1/3.9
Moviflovacin	0.00	0.5	0.015 - 4	90.070.0	90.1/2.0
Gatifloxacin	<0.00	05	<0.03 - 4	980/00	- / -
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
Moviflovacin	0.00	>0	0.013 - >8	/9.1/14.0	67 4 / 32 6
Gatifloxacin	0.0	>8	<0.12 ->0	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
	1	2	0.25 – >4	93.0 / 2.3	53.5 / 7.0
2. aeruginosa (43)	0.5	0	0.10 . 0	1	1
Ciproflovacin	0.5	0 8	0.12 ->8	-/- 682/182	-/- 63.6/31.8
Levofloxacin	0.12	0 \\8	0.00 - >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	4	>4	1 – >4	- / -	- / -
Acinetobacter spp.º (wild-type,	21)	4	0.045 4	1	1
KPI-10 Ciproflovacin	0.5	1	0.015 - 4	-/- 22.2/66.7	-/-
Levoflozacin	20	>0	0.12 - >8	33.3/00.7	33.3/00.7
Moxifloxacin	8	>8	0.00 - >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 th	ne CLSI [20	12] and EL	JCAST [2012].		

USA-FDA breakpoints were applied [Tygacil Product Insert, 2012].

Acinetobacter (2 strains).

. Includes: Enterobacter aerogenes (15 strains), E. cloacae (35 strains), and E. intermedius (1 d. Includes: Acinetobacter baumannii (18 strains), A. Iwoffii (1 strain), and unspeciated

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



- fluoroguinolones.
- UTI due to emerging fluoroquinolone-resistant E. coli.

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Robert K. Flamm, PhD **JMI Laboratories** 345 Beaver Kreek Ctr, Ste A North Liberty, Iowa, 52317, USA Phone: 319-665-3370 Email: robert-flamm@jmilabs.com

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

• The data suggest that KPI-10 merits clinical evaluation for use in UTI, including

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