Gepotidacin activity against *Escherichia coli* and *Klebsiella pneumoniae*, including molecularly characterized fluoroquinolone not susceptible subsets causing urinary tract infections in United States Medical Centers (2023)

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Gepotidacin showed activity against FQ-susceptible and FQ-not susceptible *E. coli* and *K. pneumoniae* causing UTIs in the US, particularly against isolates carrying QRDR mutations where standard oral antibiotics showed limited activity.

Digital poster

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Introduction

- Gepotidacin is a novel, bactericidal, first-in-class triazaacenaphthylene antibacterial that inhibits bacterial DNA replication by a unique mechanism of action, possesses a distinct binding site [1, 2], and provides well-balanced inhibition of two different type II topoisomerase enzymes in most pathogens causing uncomplicated urinary tract infections (uUTI) and *Neisseria gonorrhoeae*.[3, 4]
- Gepotidacin was approved earlier this year for the treatment of uUTI caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii* complex, *Staphylococcus saprophyticus*, and *Enterococcus faecalis*.[5]
- This study reports the *in vitro* activity of gepotidacin and other oral antibiotics tested against *E. coli* and *K. pneumoniae*, including molecularly characterized fluoroquinolone (FQ) not susceptible (NS) isolates collected from UTI patients in the United States.

Table 1 Frequency distribution of gepotidacin MIC values against FQ susceptible and FQ-not susceptible *E. coli* and *K. pneumoniae* from the United States

Organism (No. tested)	Number and cumulative % of isolates inhibited at a gepotidacin MIC (mg/L) of:									Gepotidacin	
Phenotype/genotype	≤0.5	1	2	4	8	16	32	64	>64	MIC_{50}	MIC_{90}
E. coli (1011)	93 9.2	373 46.1	438 89.4	82 97.5	17 99.2	8 100				2	4
FQ-S (812)	59 7.3	310 45.4	377 91.9	60 99.3	5 99.9	1 100				2	2
FQ-NS (199)	34 17.1	63 48.7	61 79.4	22 90.5	12 96.5	7 100				2	4
Non-wildtype QRDR[a] (191)	34 17.8	63 50.8	61 82.7	21 93.7	8 97.9	4 100				1	4
Non-wildtype QRDR and no PMQR[b] (159)	34 21.4	56 56.6	49 87.4	14 96.2	4 98.7	2 100				1	4
Wildtype QRDR[c] (8)				1 12.5	4 62.5	3 100				-	-
K. pneumoniae (398)		1 0.3	10 2.8	190 50.5	129 82.9	38 92.5	21 97.7	5 99.0	4 100	4	16
FQ-S (327)		1 0.3	10 3.4	181 58.7	111 92.7	19 98.5	5 100			4	8
FQ-NS (71)				9 12.7	18 38.0	19 64.8	16 87.3	5 94.4	4 100	16	64
Non-wildtype QRDR[d] (19)				8 42.1	7 78.9	2 89.5	1 94.7	1 100		8	32
Non-wildtype QRDR and no PMQR[e] (6)				5 83.3	1 100					-	-
Wildtype QRDR[f] (52)				1 1.9	11 23.1	17 55.8	15 84.6	4 92.3	4 100	16	64
Wildtype QRDR and no PMQR (9)						4 44.4	3 77.8	2 100		-	-

FQ-S, fluoroquinolone susceptible; FQ-NS, fluoroquinolone not susceptible isolates with MIC ≥0.5 µg/mL for ciprofloxacin and/or ≥1 µg/mL for levofloxacin; QRDR, quinolone resistance determining region; "-", $MIC_{50/90}$ values not calculated due to small number of isolates.
[a] For footnotes "a' through "f", refer to Table 2 for additional information.

Methods

Bacterial Isolates

- A total of 1,011 *E. coli* and 398 *K. pneumoniae* isolates responsible for UTI in patients seen in 58 sites in the USA, as part of the SENTRY Antimicrobial Surveillance Program for 2023 were included in this study.

Antimicrobial Susceptibility Testing

- Isolates were tested for susceptibility by broth microdilution following Clinical and Laboratory Standards Institute (CLSI) M07 (2024) guidelines.[6] Gepotidacin MIC values were interpreted based on the FDA susceptible breakpoint (≤16 µg/mL), whereas CLSI breakpoints were applied for comparator agents.[5, 7]

Screening of FQ Resistance Determinants

- *E. coli* and *K. pneumoniae* with MIC ≥0.5 µg/mL for ciprofloxacin and/or ≥1 µg/mL for levofloxacin (not susceptible to either agent based on CLSI criteria)[7] were selected for screening of FQ resistance mechanism.
- Isolates were subjected to genome sequencing, followed by screening of mutations in the quinolone resistance-determining regions (QRDR) of GyrA, GyrB, ParC, and ParE and plasmid-mediated FQ resistance (PMQR) genes.

Results

E. coli

- Overall, gepotidacin had $MIC_{50/90}$ values of 2/4 µg/mL against all *E. coli* and inhibited all (100%) isolates at the FDA susceptible clinical breakpoint of ≤16 µg/mL (Table 1).[5]
  - Among comparators, only nitrofurantoin (97.4% susceptible) was active against more than 90% of *E. coli* clinical isolates (Table 2).
- A total of 19.7% (199/1,011) of *E. coli* were FQ-NS, and 96.0% (191/199) of these isolates carried amino acid alterations within QRDR (Tables 1 and 2).
  - In addition, a total of 16.8% (32/191) of these FQ-NS isolates with QRDR mutations carried PMQR genes (19 *aac*(6′)-*Ib-cr*; 1 *qnrA*, 2 *qnrB*; 8 *qnrS1*; 1 *qnrB*/*qnrS* and 1 *qepA*) (Table 1).
  - A total of 8 FQ-NS *E. coli* isolates displayed wildtype QRDR, and all 8 isolates carried *qnrS1* (Table 1).
- Gepotidacin had MIC_{90} values of 4 µg/mL against FQ-NS *E. coli*, regardless of FQ resistance mechanisms (Tables 1 and 2).
  - All FQ-NS *E. coli* clinical isolates were susceptible to gepotidacin (Tables 1 and 2).
  - Nitrofurantoin was active against 93.5% of FQ-NS *E. coli* clinical isolates, whereas other comparator agents had limited activity (<80% susceptible) (Table 2).

K. pneumoniae

- Gepotidacin had $MIC_{50/90}$ of 4/16 µg/mL against all *K. pneumoniae*, and inhibited 92.5% at the FDA susceptible clinical breakpoint of ≤16 µg/mL (Table 1).[5]
  - Among comparators, amoxicillin-clavulanate showed the highest susceptibility result (90.4%) (Table 2).
- A total of 17.8% (71/398) of *K. pneumoniae* isolates were FQ-NS, and among these isolates, 73.2% (52/71) carried wildtype amino acid sequences for QRDR, whereas 26.8% (19/71) carried non-wildtype (Table 1).
  - Among the 19 *K. pneumoniae* with QRDR alterations, 68.4% (13/19) also carried PMQR genes, including *aac*(6′)-*Ib-cr* (1), *aac*(6′)-*Ib-cr*/*qnrB* (7), *aac*(6′)-*Ib-cr*/*qnrS* (1), *qnrB* (2), and *qnrS* (2).
  - In contrast, 82.7% (43/52) of the isolates with wildtype QRDR carried PMQR genes, including *aac*(6′)-*Ib-cr*/*qnrB* (13), *qnrB* (12), *qnrS* (18).
- When applying the FDA susceptible breakpoint, 64.8% of FQ-NS *K. pneumoniae* were susceptible to gepotidacin (Table 2).
- Gepotidacin inhibited 89.5% to 100% of the FQ-NS *K. pneumoniae* with QRDR mutations, regardless of the presence of PMQR (Table 2).
- Susceptibility to comparator agents was limited (≤52.1%) against all FQ-NS *K. pneumoniae.*

Table 2 Activity of gepotidacin and other oral agents tested against *E. coli* and *K. pneumoniae* UTI isolates collected from medical centers in the United States during 2023

Organism (No. tested)	MIC_{50}/MIC_{90} in µg/mL (% susceptible by CLSI)					
Phenotype/genotype	GEP	AMC	CFZ	CIP	NIT	SXT
E. coli (1011)	2/4 (100)	4/16 (88.1)	2/>32 (85.0)	0.015/>4 (80.3)	16/32 (97.4)	≤0.12/>4 (71.5)
FQ-S (812)	2/2 (100)	4/8 (90.1)	1/16 (92.4)	0.008/0.12 (100)	16/32 (98.4)	≤0.12/>4 (78.1)
FQ-NS (199)	2/4 (100)	8/16 (79.9)	8/>32 (54.8)	>4/>4 (0.0)	16/32 (93.5)	>4/>4 (44.4)
Non-WT QRDR[a] (191)	1/4 (100)	8/16 (80.1)	8/>32 (56.0)	>4/>4 (0.0)	16/32 (93.7)	>4/>4 (44.7)
Non-WT QRDR and no PMQR[b] (159)	1/4 (100)	8/16 (88.7)	4/>32 (61.6)	>4/>4 (0.0)	16/32 (96.2)	>4/>4 (45.3)
WT QRDR[c] (8)	-/- (100)	-/- (75.0)	-/- (25.0)	-/- (0.0)	-/- (87.5)	-/- (37.5)
K. pneumoniae (398)	4/16 (92.5)	2/8 (90.4)	1/>32 (82.9)	0.015/1 (82.4)	64/>128 (28.4)	≤0.12/>4 (81.4)
FQ-S (327)	4/8 (98.5)	2/4 (98.8)	1/2 (95.4)	0.015/0.06 (100)	64/>128 (30.9)	≤0.12/0.5 (93.9)
FQ-NS (71)	16/64 (64.8)	8/32 (52.1)	>32/>32 (25.4)	2/>4 (1.4)	>128/>128 (16.9)	>4/>4 (23.9)
Non-WT QRDR[d] (19)	8/32 (89.5)	16/>32 (36.8)	>32/>32 (21.1)	>4/>4 (0.0)	>128/>128 (0.0)	>4/>4 (31.6)
Non-WT QRDR and no PMQR[e] (6)	-/- (100)	-/- (33.3)	-/- (33.3)	-/- (0.0)	-/- (0.0)	-/- (66.7)
WT QRDR[f] (52)	16/64 (55.8)	8/32 (57.7)	>32/>32 (26.9)	0.5/4 (1.9)	128/>128 (23.1)	>4/>4 (21.2)
WT QRDR and no PMQR (9)	-/- (44.4)	-/- (100)	-/- (77.8)	-/- (11.1)	-/- (0.0)	-/- (55.6)

FQ-S, fluoroquinolone susceptible; FQ-NS, fluoroquinolone not susceptible isolates with MIC ≥0.5 µg/mL for ciprofloxacin and/or ≥1 µg/mL for levofloxacin; QRDR, quinolone resistance determining region; GEP, gepotidacin; AMC, amoxicillin-clavulanate; CFZ, cefazolin; CIP, ciprofloxacin; NIT, nitrofurantoin; SXT, trimethoprim-sulfamethoxazole; Gepotidacin FDA susceptible breakpoint (≤16 µg/mL) applied; CLSI breakpoints applied for comparator agents; "-", $MIC_{50/90}$ values not calculated due to small number of isolates.
[a] Includes isolates with mutation in the QRDR of GyrA (DNA gyrase subunit A), ParC (DNA topoisomerase IV subunit A) and/or ParE (DNA topoisomerase IV subunit E). A total of 16.8% (32/191) of these isolates carried PMQR genes (19 *aac*(6′)-*Ib-cr*; 1 *qnrA*, 2 *qnrB*; 8 *qnrS1*; 1 *qnrB*/*qnrS* and 1 *qepA*).
[b] Includes isolates with mutation in the QRDR of GyrA, ParC and/or ParE, and excludes 32 isolates that carried PMQR genes.
[c] Includes isolates with wildtype QRDR, but all strains carried *qnrS1*.
[d] Includes isolates with mutation in the QRDR of GyrA, ParC and/or ParE. A total of 68.4% (13/19) of these isolates carried PMQR genes (1 *aac*(6′)-*Ib-cr*; 7 *aac*(6′)-*Ib-cr*/*qnrB*, 1 *aac*(6′)-*Ib-cr*/*qnrS*, 2 *qnrB*; and 2 *qnrS*).
[e] Includes isolates with mutation in the QRDR of GyrA, ParC and/or ParE, and excludes 13 isolates that carried PMQR genes.
[f] Includes isolates with wildtype QRDR, and 82.7% (43/52) of these isolates carried PMQR genes (13 *aac*(6′)-*Ib-cr*/*qnrB*; 12 *qnrB*; 18 *qnrS*).

Conclusions

- Gepotidacin demonstrated activity, with 100% susceptibility, against both FQ-S and FQ-NS *E. coli* causing UTIs in US medical centers, regardless of FQ resistance mechanisms.
- Gepotidacin was highly active against FQ-S *K. pneumoniae* and showed activity higher than comparator agents against FQ-NS *K. pneumoniae*.
- These data benchmark gepotidacin against *E. coli* and *K. pneumoniae* for subsequent monitoring following its FDA approval for the treatment of uUTIs.

Abbreviations

CLSI, Clinical and Laboratory Standards Institute; FDA, Food and Drug Administration; FQ-NS, fluoroquinolone not susceptible; FQ-S, fluoroquinolone susceptible; I, intermediate; MIC, Minimal inhibitory concentration; NS, not susceptible; PMQR, plasmid-mediated fluoroquinolone resistance; QRDR, quinolone resistance determining region; R, resistant; S, susceptible; UTI, urinary tract infection.

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