In Vitro Activity of BWC0977 (a Novel Bacterial Topoisomerase Inhibitor) and Comparators against Recent Clinical and Molecularly **Characterized Enterobacteriaceae and Non-Fermenter Isolates from** the United States and Europe

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Introduction

- BWC0977 is a novel broad-spectrum dual-targeting bacterial topoisomerase inhibitor with potent in vitro activity against fluoroquinolone-susceptible (FQ-S) and -resistant (FQ-R) Enterobacteriaceae and non-fermenter isolates
- BWC0977 remains active against drug-resistant isolates, including aminoglycosideresistant-, extended-spectrum β-lactamase (ESBL)-, carbapenem-resistant Enterobacteriaceae (CRE)-, multidrug-resistant-, and metallo-β-lactamase-producing strains
- In this study, we tested BWC0977 and comparator agents against 1,237 recent (2017) Enterobacteriaceae and non-fermenter isolates from the United States and Europe

Materials and Methods

- A total of 1,033 Enterobacteriaceae and 204 non-fermenter (Acinetobacter baumannii and *Pseudomonas aeruginosa*) bacterial clinical isolates were collected from 106 medical centers in the United States (50.4%) and Europe (49.6%) during 2017 as part of the SENTRY Antimicrobial Surveillance Program according to a common surveillance design
- Isolates were collected from patients with bloodstream infections (24.9%), skin and skin structure infections (21.7%), pneumonia in hospitalized patients (20.4%), urinary tract infections (26.7%), intra-abdominal infections (4.9%), and other infection types (1.4%)
- All isolates were tested against BWC0977 and comparator compounds (ceftazidime, ciprofloxacin, levofloxacin, and meropenem) according to CLSI M07 (2018) reference broth microdilution methodology using frozen form panels produced by JMI Laboratories
- FQ-R Enterobacteriaceae were phenotypically defined as isolates displaying ciprofloxacin and levofloxacin minimal inhibitory concentration (MIC) values of >1 mg/L and >2 mg/L (CLSI, 2019), respectively
- ESBL Enterobacteriaceae were defined phenotypically as isolates displaying ceftazidime MIC values $\geq 2 \text{ mg/L}$
- CRE isolates were defined as displaying meropenem MIC values of >2 mg/L (CLSI, 2019)
- All categorical interpretations used CLSI M100 (2019) and EUCAST v9.0 (2019) breakpoint criteria
- Quality control (QC) ranges for reference compounds and bacterial strains were those approved or published by the CLSI (M100, 2019)

Results

- In this study, all (100.0%) of the QC values obtained were within CLSI published ranges (data not shown)
- BWC0977 (MIC₉₀, 0.5 mg/L) was the most potent topoisomerase inhibitor tested against 1,033 Enterobacteriaceae isolates from the United States and Europe compared to ciprofloxacin (MIC₉₀, 4 mg/L) and levofloxacin (MIC₉₀, 4 mg/L) (Table 1)
- BWC0977 (MIC_{50/90}, 0.25/4 mg/L) was highly active against 136 FQ-R Enterobacteriaceae isolates compared to ciprofloxacin, levofloxacin, and ceftazidime with MIC_{50/90} values of 32/128 mg/L, 8/32 mg/L, and 2/>32 mg/L, respectively (Table 1 and Figure 1)
- Enterobacteriaceae expressing an ESBL-phenotype (n=183) were inhibited by low levels of BWC0977 (MIC_{50/90}, 0.25/2 mg/L); MIC₉₀ values for ciprofloxacin and levofloxacin were 32-fold and 8-fold higher, respectively, with susceptibilities ranging from 51.4% to 55.2% (Table 1 and Figure 2)

Conclusions

- and meropenem

Acknowledgements

This study and poster presentation were funded by a grant from Bugworks Research Inc. (Wilmington, Delaware, USA).

References

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Against CRE, BWC0977 (MIC₉₀, 2 mg/L) was 32-fold, 8-fold, and >8-fold more active than profloxacin, levofloxacin, and meropenem, respectively (MIC₉₀ values of 64 mg/L, 16 mg/L, and >16 mg/L respectively) (Table 1)

BWC0977 was highly active against Escherichia coli (MIC_{50/90}, 0.12/0.5 mg/L), Klebsiella pneumoniae (MIC_{50/90}, 0.25/2 mg/L), Morganella morganii (MIC_{50/90}, 0.12/0.25 mg/L), and Proteus mirabilis (MIC_{50/90}, 0.12/0.5 mg/L) isolates whereas susceptibility to ciprofloxacin (MIC₉₀, 8-64 mg/L; 63.7% to 73.3% susceptible) and levofloxacin (MIC₉₀, 8-32 mg/L; 66.7% to 75.2% susceptible) was reduced (Table 1)

Citrobacter spp., Enterobacter spp., Klebsiella oxytoca, and Serratia marcescens isolates were inhibited by low levels of BWC0977 (MIC_{50/90}, 0.12-0.25/0.25-2 mg/L) (Table 1)

BWC0977 was the most active compound tested against non-fermenter isolates including Acinetobacter baumannii (MIC_{50/90}, 0.25/0.5 mg/L) and Pseudomonas aeruginosa (MIC_{50/90}, 0.5/2 mg/L) (Table 1 and Figure 3)

Reduced susceptibility was noted for ceftazidime (MIC_{50/90}, 16/>32 mg/L; 48.5% susceptible), ciprofloxacin (MIC_{50/90}, 2/>128 mg/L; 47.6% susceptible), levofloxacin (MIC_{50/90}, 1/64 mg/L; 48.5% susceptible), and meropenem (MIC_{50/90}, 2/>16 mg/L; 56.3% susceptible) against A. baumannii isolates (Table 1 and Figure 3)

BWC0977 was the most potent bacterial topoisomerase inhibitor tested against Enterobacteriaceae (MIC_{50/90}, 0.25/0.5 mg/L) isolates

BWC0977 was highly active against resistant organism groups, including FQ-R Enterobacteriaceae (MIC_{50/90}, 0.25/4 mg/L), ESBL-phenotype Enterobacteriaceae (MIC_{50/90}, 0.25/2 mg/L), and CRE (MIC_{50/90}, 0.5/2 mg/L) strains

Against non-fermenters, BWC0977 was the most active compound tested against A. baumannii (MIC_{50/90}, 0.25/0.5 mg/L) and *P. aeruginosa* (MIC_{50/90}, 0.5/2 mg/L) isolates and outperformed comparator agents including ceftazidime, ciprofloxacin, levofloxacin,

BWC0977 is a new, novel, dual targeting bacterial topoisomerase inhibitor with potent Gram-negative antibacterial activity including activity against strains demonstrating resistance to multiple drug classes

Additional studies are needed to investigate the utility of BWC0977 in difficult-to-treat resistant Gram-negative infections

Table 1 Antimicrobial activity of BWC0977 and comparators against 1,237 Enterobacteriaceae and non-fermenter isolates from the 2017 SENTRY Program (United States and Europe)

Organism/organism group (no.)	MIC	MIC	Range	CLSI/E	UCAST ^a
Antimicrobial agent Enterobacteriaceae (1.033) ^b	50	90		% S	%R
BWC0977	0.25	0.5	<0.015 to >32		
Ciprofloxacin	≤0.06	4	≤0.06 to >128	83.2/83.2	15.2/15.2
Levofloxacin	≤0.06	4	≤0.06 to >128	84.3/84.3	13.4/13.4
Ceftazidime	0.25	32	≤0.03 to >32	85.3/82.3	13.2/14.7
RWC0977	0.25	_	0.03 to >32		
Ciprofloxacin	32	128	1 to >128	0.0/0.0	100.0/100.0
Levofloxacin	8	32	2 to >128	0.0/0.0	100.0/100.0
Ceftazidime	2	>32	2 to >32	54.4/45.6	37.5/45.6
ESBL-phenotype Enterobacteriaceae (183) ^d	0.05				
Ciprofloxacin	0.25	2 64	$\leq 0.015 \ 10 > 32$		
Levofloxacin	0.5	16	≤0.06 to >128	55.2/55.2	41.0/41.0
Ceftazidime	>32	>32	2 to >32	16.9/0.0	74.3/83.1
CRE (10) ^e					
BWC0977	0.5	2	0.12 to 4		
	<u>≤0.06</u> 0.12	16	$\leq 0.06 \text{ to } 128$	50.0/50.0	50.0/50.0
Meropenem	8	>16	4 to >16	0.0/0.0	100.0/100.0
Citrobacter koseri (105)				,	
BWC0977	0.12	0.25	≤0.015 to 1	_	_
Ciprofloxacin	≤0.06	≤0.06	≤0.06 to 0.25	100.0/100.0	0.0/0.0
Levofloxacin	<u>≤0.06</u> 0.12	≤0.06	$\leq 0.06 \text{ to } 0.5$	100.0/100.0	0.0/0.0 12.2/14.7
Citrobacter freundii species complex (103)	0.12	0.5	<u>≤0.05 (0 >32</u>	03.3/02.3	13.2/14.7
BWC0977	0.25	1	0.06 to 8	_	_
Ciprofloxacin	≤0.06	0.5	≤0.06 to 32	89.3/89.3	6.8/6.8
Levofloxacin	≤0.06	0.5	≤0.06 to 32	91.3/91.3	6.8/6.8
Ceftazidime	0.5	>32	0.06 to >32	(2.8/(2.8	21.4/21.4
BWC0977	0.25	0.5	<0.015 to 16	_	
Ciprofloxacin	≤0.06	0.12	≤0.06 to 8	94.1/94.1	4.9/4.9
Levofloxacin	≤0.06	0.5	≤0.06 to 8	95.1/95.1	3.9/3.9
Ceftazidime	0.5	>32	0.06 to >32	65.7/65.7	31.4/31.4
Enterobacter cloacae species complex (107)	0.25	2	$0.02 t_0 > 22$		
Ciprofloxacin	<0.06	2	<0.03 to >32 <0.06 to >128	- 84 1/84 1	- 15 9/15 9
Levofloxacin	<u>≤0.06</u>	2	≤0.06 to 128	85.0/85.0	14.0/14.0
Ceftazidime	0.5	>32	0.12 to >32	63.6/63.6	32.7/32.7
Escherichia coli (102)					
BWC0977 Ciproflexeein	0.12	0.5	0.03 to 4	-	
Levofloxacin	<u>≤0.06</u>	16	<0.06 to 32	66 7/66 7	32 4/32 4
Ceftazidime	0.25	8	0.06 to >32	83.3/83.3	14.7/14.7
Klebsiella oxytoca (104)				1	
BWC0977	0.12	0.5	0.03 to 2	-	-
Ciprofloxacin	≤0.06	≤0.06	≤0.06 to 2	98.1/98.1	1.9/1.9
Ceftazidime	<u>≤0.06</u> 0.12	≤0.00	$\leq 0.00 \text{ to } 0.3$	96 2/96 2	29/29
Klebsiella pneumoniae (103)					
BWC0977	0.25	2	0.06 to 8	—	_
Ciprofloxacin	≤0.06	64	≤0.06 to >128	71.8/71.8	26.2/26.2
Levofloxacin	≤0.06	8	$\leq 0.06 \text{ to } > 128$	(2.8/(2.8	22.3/22.3
Morganella morganii (101)	0.25	>32	0.00 to >32	13.0/13.0	23.2/23.2
BWC0977	0.12	0.25	≤0.015 to 2	_	_
Ciprofloxacin	≤0.06	8	≤0.06 to 128	73.3/73.3	23.8/23.8
Levofloxacin	≤0.06	8	≤0.06 to 32	75.2/75.2	19.8/19.8
Ceftazidime	0.25	4	≤0.03 to 32	83.2/83.2	9.9/9.9
BWC0977	0.12	0.5	0.03 to 2		
Ciprofloxacin	≤0.06	32	≤0.06 to >128	68.0/68.0	32.0/32.0
Levofloxacin	0.12	32	≤0.06 to 128	68.0/68.0	30.1/30.1
Ceftazidime	0.06	0.12	≤0.03 to 32	95.1/95.1	2.9/2.9
Serratia marcescens (103)	0.25	1	0.06 to 22		
Ciprofloxacin	<0.06	L 0.5	<0.06 to 8		- 7 8/7 8
Levofloxacin	0.12	1	≤0.06 to 8	88.3/88.3	4.9/4.9
Ceftazidime	0.25	0.5	0.06 to >32	91.3/91.3	4.9/4.9
Acinetobacter baumannii (103)					
BWC0977 Ciproflovooin	0.25	0.5	0.03 to 4		
Levofloxacin	1	>128	<0.12 to >128 <0.06 to >128	47.0/47.0	52.4/52.4 48.5/48.5
Ceftazidime	16	>32	2 to >32	48.5/-	48.5/-
Meropenem	2	>16	0.12 to >16	56.3/56.3	42.7/41.7
Pseudomonas aeruginosa (101)					
BWC0977	0.5	2	≤0.015 to 8	-	-
	0.12	4	≤0.06 to >128	76.2/76.2 68.2/68.2	23.8/23.8
Ceftazidime	2	16	0.12 to 120 0.06 to >32	87.1/87.1	7.9/12.9
Meropenem	0.5	16	0.008 to >16	83.2/83.2	13.9/5.0

Criteria as published by CLSI 2019 and EUCAST 2019

^o Organisms include: Citrobacter freundii species complex (103), C. koseri (105), Enterobacter aerogenes (102), E. cloacae species complex (107), Escherichia coli (104), K. pneumoniae (103), Morganella morganii (101), Proteus mirabilis (103), Serratia marcescens (103). ° Organisms include: Citrobacter freundii species complex (6), Enterobacter aerogenes (4), E. cloacae species complex (15), Escherichia coli (33), Klebsiella pneumoniae (23), Morganella morganii (20), Proteus mirabilis (31), Serratia marcescens (4). ^d Organisms include: Citrobacter freundii species complex (28), C. koseri (2), Enterobacter aerogenes (35), E. cloacae species complex (39), Escherichia coli (17), Klebsiella oxytoca (4), K. pneumoniae (27), Morganella morganii (17), Proteus mirabilis (5), Serratia marcescens (9). ^e Organisms include: Enterobacter aerogenes (3), E. cloacae species complex (2), Escherichia coli (1), K. pneumoniae (3), Serratia marcescens (1). FQ-R, fluoroquinolone-resistant; ESBL, extended-spectrum β -lactamase; CRE, carbapenem-resistant Enterobacteriaceae

Figure 1 In vitro activity of BWC0977 and comparators against 136 fluoroquinolone-resistant Enterobacteriaceae isolates



Figure 2 In vitro activity of BWC0977 and comparators against 183 extended-spectrum β -lactamase-phenotype Enterobacteriaceae



Figure 3 In vitro activity of BWC0977 and comparators against 103 Acinetobacter baumannii isolates



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