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In Vitro Activity of the β-lactamase Inhibitor QPX7728 in Combination with Several β-lactams against *Acinetobacter baumannii* (AB) and *Pseudomonas aeruginosa* (PSA)

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Abstract

Background: QPX7728 (QPX) is a novel broad-spectrum boron-containing inhibitor of serine- and metallo-β-lactamases (MBLs). We evaluated the *in vitro* activity of QPX combined with several β-lactams against carbapenem-resistant AB (CRAB) and PSA clinical isolates with varying β-lactam resistance mechanisms.

Methods: A total of 503 CRAB (meropenem [MEM] MIC ≥8 µg/ml) and 762 PSA clinical isolates were tested by the reference broth microdilution method against β-lactams alone and combined with QPX (4 µg/ml and 8 µg/ml). PSA isolates were selected to represent the normal distribution of MEM, ceftazidime-avibactam (CAZ-AVI), and ceftolozane-tazobactam (TOL-TAZ) resistance according to 2017 surveillance data (representative panel). Additionally, 262 PSA isolates that were either non-susceptible (NS) to MEM (MIC, ≥4 µg/ml) or to TOL-TAZ (MIC, ≥8 µg/ml), or resistant (R) to CAZ-AVI (MIC, ≥16 µg/ml) (challenge panel) were also tested. Within this 262 strain challenge set, 56 strains carried MBLs and the majority also had non-functional OprD.

Results: Against CRAB, QPX at 4 µg/ml and 8 µg/ml increased the potency of all β-lactams tested. MEM-QPX was the most potent combination (Table) displaying MIC_{50}/MIC_{90} at 1/8 µg/ml and 0.5/4 µg/ml with QPX at fixed 4 µg/ml and 8 µg/ml, respectively. Susceptibility (S) to MEM was restored in >95% of strains. Against the 500 PSA from the representative panel, S for all QPX combinations was >90%. For the challenge panel, TOL-QPX and piperacillin (PIP)-QPX were the most potent combinations, restoring S in 76-77% of strains. TOL-QPX and MEM-QPX or cefepime (FEP)-QPX restored the MIC values to S rates when applying the CLSI breakpoint for the compound alone (comparison purposes only) in ~90% and ~75% of non-MBL-producing strains, respectively, vs 60-70% for TOL-TAZ and CAZ-AVI. PIP-QPX reduce the MIC values to S values for PIP-TAZ in ~60% of MBL-producing strains vs 20-30% and 3-7% for other QPX combinations and non-QPX tested combinations, respectively.

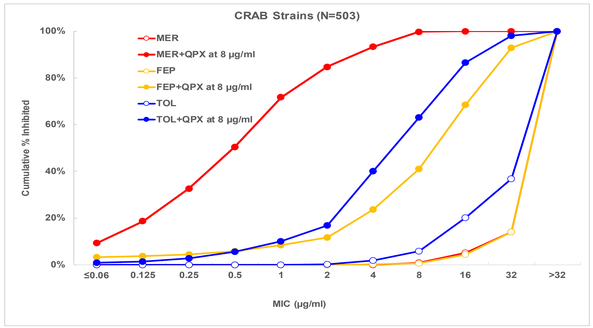
Conclusions: Combinations of QPX with various β-lactam antibiotics displayed potent activity against CRAB and resistant PSA isolates and warrant further investigation.

.	MIC_{50}/MIC_{90} (µg/ml) (% inhibited at the β-lactam alone breakpoint for CLSI [for comparison only])								
	MEM	MEM-QPX	TOL-TAZ	TOL-QPX	FEP	FEP-QPX	PIP-TAZ	PIP-QPX	CAZ-AVI
CRAB (503)	>32/>32	0.5/4	32/>32	8/32	>32/>32	16/32	ND	ND	ND
	(1.0)	(99.8)	(2.0)	(40.2)	(0.6)	(41.2)			
PSA (500), representative panel	0.5/16	0.25/8	0.5/4	0.5/1	4/32	2/8	8/128	ND	2/8
	(84.8)	(91.6)	(91.8)	(97.6)	(74.4)	(90.2)	(71.6)		(92.2)
PSA (262), challenge panel	16/>64	4/>64	8/>64	1/>64	32/>64	8/>64	128/>256	16/32	16/>64
	(41.6)	(66.0)	(48.9)	(77.1)	(19.8)	(64.9)	(16.8)	(76.0)	(48.0)
PA (no MBL) (206)	8/64	4/16	4/>64	1/4	32/>64	8/16	128/>256	8/32	8/64
	(51.0)	(75.7)	(60.7)	(91.7)	(24.3)	(76.2)	(19.4)	(80.1)	(61.2)
PA (MBL) (56)	>64/>64	64/>64	>64/>64	>64/>64	>64/>64	64/>64	128/>256	16/64	>64/>64
	(7.1)	(30.4)	(5.4)	(23.2)	(3.6)	(23.2)	(7.1)	(60.7)	(3.6)

QPX7728 at 8 µg/ml; AVI and TAZ at 4 µg/ml.

Results

Figure 1. MIC Distribution of QPX7728 Combinations against Carbapenem-Resistant *A. baumannii*



MER, meropenem; TOL, ceftolozane; FEP, cefepime

Table 1. MIC Distributions of QPX7728 Combinations for the Representative Panel of *P. aeruginosa* (N=500)

MIC (µg/ml)	MER	MER+QPX at 4 µg/ml	MER+QPX at 8 µg/ml	TOL	TOL+TAZ	TOL+QPX at 4 µg/ml	TOL+QPX at 8 µg/ml	CAZ+AVI
≤0.06	4.8%	9.0%	10.8%	0.2%	0.0%	0.6%	2.4%	0.2%
0.125	14.2%	26.0%	29.0%	0.2%	0.2%	2.6%	3.4%	0.2%
0.25	33.0%	47.8%	**50.8%**	2.8%	3.6%	8.0%	13.2%	0.8%
0.5	**51.0%**	**61.0%**	62.6%	**56.2%**	**55.8%**	**66.0%**	**69.6%**	4.0%
1	66.2%	70.6%	71.6%	77.4%	80.6%	89.2%	**91.2%**	28.4%
2	73.2%	82.0%	82.8%	85.2%	88.6%	**93.8%**	96.4%	**66.8%**
4	79.8%	85.8%	86.4%	**90.4%**	**91.8%**	95.6%	97.6%	82.4%
8	84.8%	**91.0%**	**91.6%**	92.2%	93.8%	97.4%	97.8%	**92.2%**
16	**90.4%**	95.8%	96.2%	93.0%	93.8%	98.2%	98.2%	94.8%
32	95.4%	98.0%	98.2%	93.2%	99.8%	98.4%	98.4%	97.0%
>32	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

MER, meropenem; TOL, ceftolozane; CAZ, ceftazidime; AVI, avibactam, TAZ, tazobactam. AVI and TAZ at 4 µg/ml; numbers corresponding to MIC_{50} and MIC_{90} bolded and respective cells are labeled with yellow and green color, respectively

Table 2. MIC Distributions of QPX7728 Combinations for the Challenge Panel of *P. aeruginosa* (N=262)

	No MBL (N-206)								MBL (N-56)							
MIC (µg/ml)	MER	MER+ QPX	FEP	FEP+ QPX	TOL-TAZ	TOL+ QPX	PIP-TAZ	PIP+ QPX	MER	MER+ QPX	FEP	FEP+ QPX	TOL-TAZ	TOL+ QPX	PIP-TAZ	PIP+ QPX
≤0.06	0.0%	1.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
0.125	0.5%	1.9%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
0.25	0.5%	3.4%	0.0%	0.0%	1.9%	2.9%	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.8%
0.5	1.0%	7.3%	0.0%	1.0%	9.2%	38.8%	0.5%	1.9%	0.0%	5.4%	0.0%	0.0%	0.0%	3.6%	0.0%	3.6%
1	1.9%	14.1%	0.5%	2.9%	32.5%	**78.2%**	0.5%	3.9%	0.0%	7.1%	0.0%	0.0%	0.0%	1.8%	8.9%	1.8%	3.6%
2	2.4%	32.5%	4.9%	12.1%	48.1%	88.3%	1.0%	8.7%	0.0%	7.1%	0.0%	1.8%	5.4%	10.7%	3.6%	3.6%
4	28.2%	**55.3%**	10.7%	32.0%	**60.7%**	**91.7%**	4.4%	28.6%	0.0%	17.9%	0.0%	10.7%	5.4%	23.2%	3.6%	12.5%
8	**51.0%**	75.7%	24.3%	**76.2%**	68.4%	93.2%	13.1%	**51.0%**	7.1%	30.4%	3.6%	23.2%	5.4%	30.4%	5.4%	33.9%
16	70.9%	**91.3%**	42.7%	**94.2%**	73.3%	96.1%	19.4%	80.1%	10.7%	39.3%	7.1%	37.5%	5.4%	37.5%	7.1%	**60.7%**
32	84.0%	96.1%	**67.0%**	97.6%	82.0%	97.1%	30.6%	**94.7%**	19.6%	46.4%	17.9%	44.6%	7.1%	41.1%	16.1%	85.7%
64	**90.3%**	98.5%	79.1%	99.5%	86.9%	98.1%	46.6%	98.5%	25.0%	**53.6%**	25.0%	**51.8%**	10.7%	48.2%	30.4%	98.2%
128	100.0%	100.0%	100.0%	100.0%	**100.0%**	99.5%	**60.2%**	99.5%	**100.0%**	100.0%	**100.0%**	100.0%	**100.0%**	**100.0%**	**50.0%**	98.2%
256	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	84.5%	99.5%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	76.8%	98.2%
>256	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	**100.0%**	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

MER, meropenem; TOL, ceftolozane; FEP, cefepime, PIP, piperacillin,TAZ, tazobactam. QPX and TAZ at 8 µg/m and 4, respectively; numbers corresponding to MIC_{50} and MIC_{90} bolded and respective cells are labeled with yellow and green color, respectively

Table 3. Activity of QPX7728 Combinations Against "Challenge" Strains of *P. aeruginosa* at the Patient Level

Strain	Beta-Lactamase	OprD Status	MER	MER+QPX	FEP	FEP+QPX	TOL-TAZ	TOL+QPX	PIP-TAZ	PIO+QPX
PAM3239	VIM-1	NF	>64	8	>64	32	>64	64	>256	8
PA5439	GES-1-5(ec); KPC-2; IMP-15;	NF	>64	64	>64	>64	>64	>64	>256	8
PA5391	IMP-6;	NF	>64	>64	>64	>64	>64	>64	128	8
PA5428	KPC-2; VIM-2;	NF	>64	16	>64	16	>64	8	>256	16
PA5436	VEB-9;	NF	64	16	>64	16	>64	16	128	16
PA5435	VEB-9;	NF	>64	16	>64	16	>64	16	>256	16
PA5313	VIM-46;	NF	>64	>64	>64	32	>64	32	256	16
PA5312	IMP-48;	NF	>64	>64	>64	>64	64	64	256	16
PA5314	VEB-11; IMP-14;	FL	32	32	>64	>64	>64	>64	128	16
PA5318	IMP-62;	NF	>64	>64	>64	>64	>64	>64	32	16
PA 1064	IMP-13	NF	>64	>64	>64	>64	>64	>64	64	16
PA5266	IMP-1	NF	>64	>64	>64	>64	>64	>64	64	16
PA5277	OXA-488;IMP-1;PDC-12	NF	>64	>64	>64	>64	>64	>64	256	16
PA5278	OXA-488;IMP-1;PDC-12;OXA	NF	>64	>64	>64	>64	>64	>64	256	16
PA5471	IMP-7;	FL	>64	>64	>64	>64	>64	>64	256	16
PA5274	OXA-488;IMP-1;PDC-12;OXA	NF	>64	>64	>64	>64	>64	>64	>256	16
PA5358	PER-1;	FL	16	16	64	16	64	2	128	32
PA5358	PER-1;	FL	16	16	64	16	64	2	128	32
PA5282	OXA-486-like;CTX-M-3;PDC-	NF	16	8	>64	16	64	4	>256	32
PA5419	ND	NF	32	16	64	16	8	1	>256	64
PA5426	ND	NF	32	32	32	32	8	2	256	64
PA5459	ND	NF	64	64	32	32	64	2	64	64
PA 1069	GIM-1	FL	>64	64	16	4	32	8	256	64

Summary

- QPX7728 restored the activity of meropenem against CRAB: >90% of isolates were inhibited by ≤8 µg/ml of meropenem with QPX7728 at 4 and 8 µg/ml.
- MER+QPX7728 and TOL+QPX7728 exhibited excellent potency against a representative panel of *P. aeruginosa* that reflects the current MIC distributions. TOL+QPX7728 was more potent than MER+QPX7728, TOL-TAZ and CAZ-AVI against this panel of isolates.
- TOL+QPX7728 was also the most potent combination against the challenge panel of *P. aeruginosa* enriched with ceftazidime-avibactam resistant and ceftolozane-tazobactam or meropenem non-susceptible isolates that did not produce metallo-beta-lactamases.
- PIP+QPX7728 was the most potent combination against MBL producers.
- The optimal beta-lactam for use in combination may vary according to the beta-lactamase and other intrinsic resistance mechanisms.

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