Poster #P1181

Selection of ceftibuten as the partner antibiotic for the oral β-lactamase inhibitor VNRX-7145

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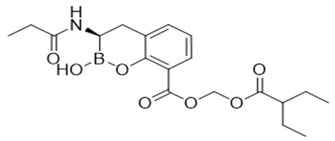
Background

β-lactams are the most widely used antibiotic class in both community and hospital settings. However, their utility against gram-negative pathogens is being threatened by the spread of new β-lactamases[1,2]. Considering there have been no new protected oral β-lactams since the discovery of amoxicillin-clavulanate in the 1980s, and that resistance to amoxicillin-clavulanate is on the rise, there is a clear need for new oral agents that avoid today's clinically-important β-lactamases[3].

VNRX-7145 is a novel cyclic boronate-based β-lactamase inhibitor with oral bioavailability in several pre-clinical species. *In vivo*, VNRX-7145 undergoes biotransformation to the active BLI, VNRX-5236, which has potent inhibitory activity against Ambler Class A, C, and D enzymes, including those that hydrolyze carbapenems. When combined with oral β-lactams, VNRX-5236 is able to restore antibacterial activity against MDR Enterobacteriaceae. Here, broth microdilution assays were utilized to investigate nine commercially available oral β-lactam antibiotics in combination with VNRX-5236 to select the one with the best overall antibacterial profile.

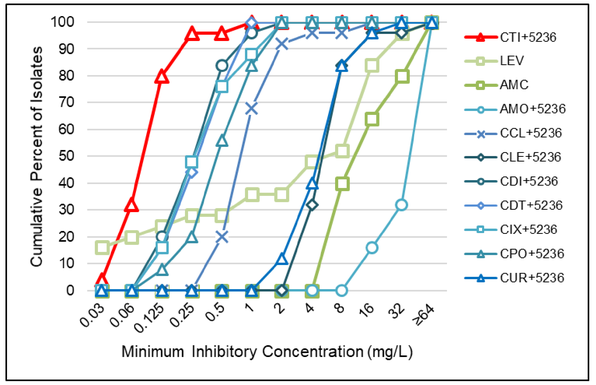
Structure of VNRX-7145



Methods

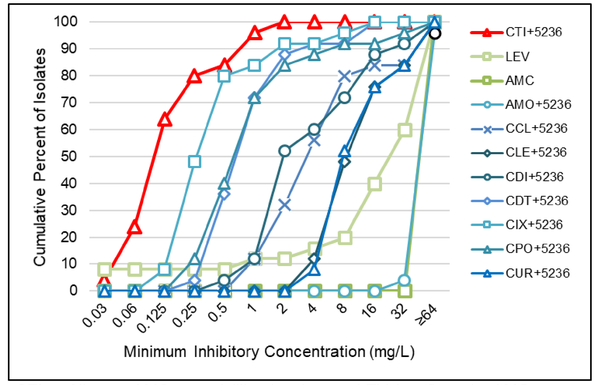
- Broth microdilution minimum inhibitory concentration assays were performed according to CLSI methods[4,5] with amoxicillin, cefaclor, cefalexin, cefdinir, cefditoren, cefixime, cefpodoxime, ceftibuten, and cefuroxime alone or in combination with VNRX-5236 fixed at 4 mg/L. Levofloxacin and amoxicillin-clavulanate were also tested as comparators.
- One hundred representative isolates were chosen from VenatoRx's in-house collection of Enterobacteriaceae expressing Class A ESBL (n=25), Class A KPC (n=25), Class C (n=25), and Class D OXA-48 (n=25) enzymes. β-lactamase genes were verified using polymerase chain reaction (PCR) while expression of these genes was determined phenotypically.
- Briefly, nine commercially available oral β-lactam antibiotics were titrated (tested range 0.016 to 32 mg/L) across 96-well microtiter plates and were mixed with either cation adjusted Mueller Hinton broth (CAMHB), or VNRX-5236 supplemented CAMHB at 4 mg/L. Levofloxacin and amoxicillin-clavulanate (2:1 ratio) were also tested (range 0.016 to 32 mg/L and 0.06 to 128 mg/L, respectively). Bacterial inocula at a final concentration of 2-5x10^5 CFU/mL were used. Microtiter plates were incubated aerobically at 37°C for 18-20 hours and MICs were read visually.

Comparative Activity Against ESBL-Expressing Isolates (n=25)



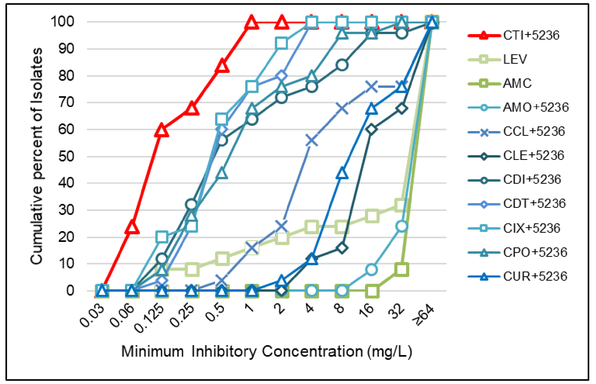
CTI, ceftibuten; AMC, amoxicillin-clavulanate; LEV, levofloxacin; AMO, amoxicillin; CCL, cefaclor; CLE, cefalexin; CDI, cefdinir; CDT, cefditoren; CIX, cefixime; CPO, cefpodoxime; CUR, cefuroxime

Comparative Activity Against OXA-Expressing Isolates (n=25)



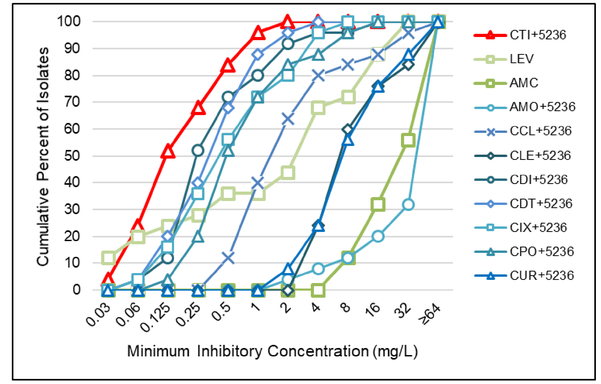
CTI, ceftibuten; AMC, amoxicillin-clavulanate; LEV, levofloxacin; AMO, amoxicillin; CCL, cefaclor; CLE, cefalexin; CDI, cefdinir; CDT, cefditoren; CIX, cefixime; CPO, cefpodoxime; CUR, cefuroxime

Comparative Activity Against KPC-Expressing Isolates (n=25)



CTI, ceftibuten; AMC, amoxicillin-clavulanate; LEV, levofloxacin; AMO, amoxicillin; CCL, cefaclor; CLE, cefalexin; CDI, cefdinir; CDT, cefditoren; CIX, cefixime; CPO, cefpodoxime; CUR, cefuroxime

Comparative Activity Against Class C-Expressing Isolates (n=25)



CTI, ceftibuten; AMC, amoxicillin-clavulanate; LEV, levofloxacin; AMO, amoxicillin; CCL, cefaclor; CLE, cefalexin; CDI, cefdinir; CDT, cefditoren; CIX, cefixime; CPO, cefpodoxime; CUR, cefuroxime

MIC_{50} and MIC_{90} Summary by Enzyme Class

β-lactam	BLI	All		ESBL		KPC		OXA		Class C	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Ceftibuten	-	16	≥64	4	≥64	16	≥64	16	≥64	16	≥64
	VNRX-5236	**0.125**	**1**	**0.125**	**0.25**	**0.125**	**1**	**0.125**	**1**	**0.125**	**1**
Amoxicillin	Clavulanate	64	≥256	16	≥64	≥64	≥256	≥256	≥256	32	≥256
Levofloxacin	-	16	≥64	8	32	≥64	≥64	32	≥64	4	32
Amoxicillin	-	≥256	≥256	≥256	≥256	≥64	≥256	≥256	≥256	≥256	≥256
	VNRX-5236	64	≥256	64	≥256	≥64	≥256	≥256	≥256	64	≥256
Cefaclor	-	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64
	VNRX-5236	2	≥64	1	2	4	≥64	4	≥64	2	32
Cefalexin	-	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64
	VNRX-5236	8	≥64	8	16	16	≥64	16	≥64	8	≥64
Cefdinir	-	≥64	≥64	32	≥64	≥64	≥64	≥64	≥64	32	≥64
	VNRX-5236	0.5	16	0.5	1	0.5	16	2	32	0.25	2
Cefditoren	-	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64
	VNRX-5236	0.5	2	0.5	1	0.5	4	1	4	0.5	2
Cefixime	-	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64
	VNRX-5236	0.5	2	0.5	2	0.5	2	0.5	2	0.5	4
Cefpodoxime	-	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64
	VNRX-5236	1	8	0.5	2	1	8	1	8	0.5	8
Cefuroxime	-	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64
	VNRX-5236	8	≥64	8	16	16	≥64	8	≥64	8	≥64

Conclusions

- The lowest MIC_{50} and MIC_{90} values were observed for VNRX-5236 combined with ceftibuten relative to all other oral β-lactams tested across all enzyme sub groups.
- Ceftibuten in combination with VNRX-5236 was more potent than either levofloxacin or amoxicillin-clavulanate across all enzyme sub groups tested.
- The overall MIC_{90} of ceftibuten-VNRX-5236 was 1 mg/L. This was even lower in ESBL producing strains with an MIC_{90} of 0.25 mg/L.
- The high absorption and favourable PK profile of ceftibuten in humans makes it the optimal oral β-lactam to partner with VNRX-7145.

References

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