

Activity of an Investigational Polymyxin-B-Like Compound (SPR206) against a Set of *Enterobacteriaceae* Organisms Responsible for Human Infections

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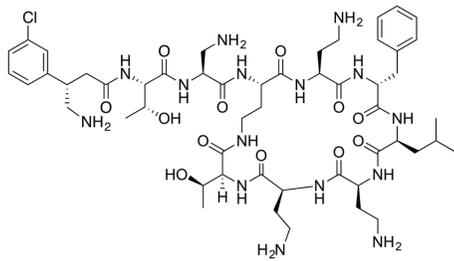
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Introduction

- Gram-negative bacteria producing extended-spectrum β -lactamase (ESBL) and/or carbapenemase enzymes that show resistance to many antibiotics have been steadily increasing to alarming levels in hospital and community settings
- SPR206 is a next-generation polymyxin compound being developed for treating infections caused by gram-negative organisms (Figure 1)
- This study evaluated the *in vitro* potency of SPR206 and compared its potency to those of polymyxin-B and colistin against *Enterobacteriaceae*, including carbapenem-resistant (CRE) organisms

Figure 1 Structure of SPR206



Results

- SPR206 (MIC_{50/90}: 0.06/0.12 mg/L) was more potent than colistin and polymyxin-B (MIC_{50/90}: 0.25/0.25 mg/L; Table 1, Figures 2 and 3)
 - SPR206 inhibited 93.2% of all *Enterobacteriaceae* at ≤ 0.12 mg/L, while colistin and polymyxin-B inhibited 38.3% and 33.1%, respectively, at ≤ 0.12 mg/L (Table 1)
- SPR206 had an MIC₁₀₀ of ≤ 2 mg/L against *Escherichia*, *Citrobacter*, *Salmonella*, and *Shigella* species (Table 1)
- Ceftriaxone displayed a bimodal MIC distribution (MIC_{50/90}: ≤ 0.12 / >8 mg/L) against all *Enterobacteriaceae* isolates and 77.4% were susceptible at the CLSI and EUCAST breakpoints of ≤ 1 mg/L
- Meropenem was very active (MIC_{50/90}: ≤ 0.12 / ≤ 0.12 mg/L) against these isolates and 97.0%/97.2% were susceptible at the CLSI/EUCAST breakpoints, respectively (Table 1)
- Against a CRE challenge set, SPR206 (MIC_{50/90}: 0.06/0.12 mg/L) showed MIC values 4-fold lower than colistin and polymyxin-B (MIC_{50/90}: 0.25/0.5 mg/L; Table 1)
 - Isolates included *bla*_{KPC}, *bla*_{NDM}, *bla*_{VIM}, and *bla*_{OXA-48} genotypes
 - MIC results similar to the random selection set are seen in Table 1
 - As expected, ceftriaxone (MIC_{50/90}: >8 / >8 mg/L) and meropenem (MIC_{50/90}: >8 / >8 mg/L) showed little activity against this challenge set (Table 1)

References

- Clinical and Laboratory Standards Institute (2018). *M100Ed28E. Performance standards for antimicrobial susceptibility testing: 28th informational supplement*. Wayne, PA: CLSI.
- Clinical and Laboratory Standards Institute (2018). *M07Ed11E. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—eleventh edition*. Wayne, PA: CLSI.
- EUCAST (2018). Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0, January 2018. Available at http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf. Accessed January 2018.

Figure 2 Comparison of colistin to SPR206 when tested against 573 *Enterobacteriaceae* isolates

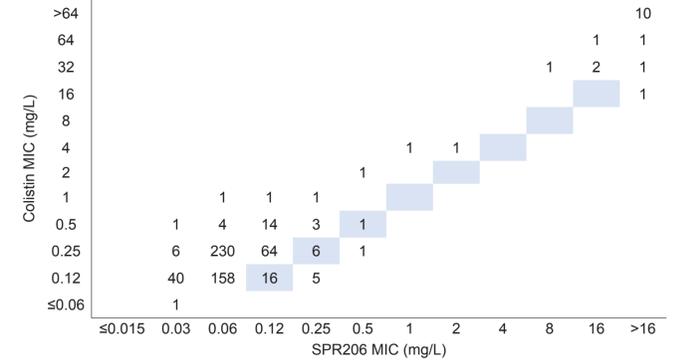
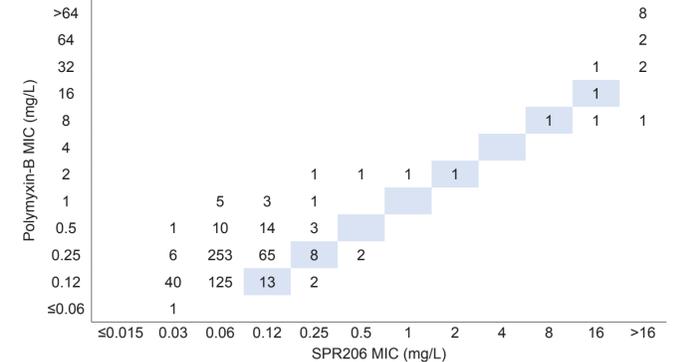


Figure 3 Comparison of polymyxin-B to SPR206 when tested against 573 *Enterobacteriaceae* isolates



Materials and Methods

Bacterial isolates

- A total of 541 recent clinical *Enterobacteriaceae* isolates (2016–2017) were randomly selected through the SENTRY Antimicrobial Surveillance Program from 150 medical centers worldwide
- Isolates were responsible for bloodstream (30%), urinary tract (26%), pneumonia (20%), skin and skin structure (15%), and other infections (9%)
- Drug activities were also investigated against an independent challenge set of 32 CRE isolates (Table 1)
- Isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa)
- Bacterial isolate identification was confirmed by standard algorithms supported by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following guidelines in the CLSI M07 (2018) document
- Frozen-form reference 96-well panels manufactured by JMI Laboratories were used for testing
- Breakpoint criteria for comparator agents were from the CLSI M100 (2018) and EUCAST (2018) documents

Conclusions

- Overall, SPR206 was highly potent against a contemporary collection of *Enterobacteriaceae* isolates
- Based on MIC_{50/90} results, SPR206 potency was consistently 2- to 4-fold greater than the potency of colistin and polymyxin-B
- Against a challenge set of isolates with increased carbapenem MIC values:
 - SPR206 MIC results were not adversely affected when compared with the MIC values obtained against randomly selected organisms.
 - SPR206 MIC values were consistently lower than colistin and polymyxin-B
- These *in vitro* results obtained for SPR206 warrant its further development as an option for treating gram-negative infections

Acknowledgements

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Table 1 Antimicrobial activity of SPR206 and comparators tested against the main organisms and organism groups

Organism group (no. of isolates)	No. and cumulative % of isolates at MIC (mg/L) of ^a :														MIC ₅₀	MIC ₉₀	EUCAST %S					
	≤ 0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	$>^b$								
Enterobacteriaceae (541)																						
SPR206	47	8.7	370	77.1	87	93.2	15	95.9	3	96.5	1	96.7	1	96.9	0	97.0	13	100.0	0.06	0.12		
Colistin			1	0.2	206	38.3	293	54.2	18	63.3	3	66.5	1	67.6	2	69.7	10	100.0	0.25	0.25	96.5	
Polymyxin-B			1	0.2	178	33.1	310	57.3	25	61.4	6	64.0	4	66.0	3	68.0	8	100.0	0.25	0.25		
Ceftriaxone					348	64.3	42	72.1	21	76.0	8	77.4	3	78.0	3	78.6	6	100.0	≤ 0.12	>8	77.4	
Meropenem					516	95.4	6	96.5	3	97.0	0	97.2	1	97.2	0	97.4	14	100.0	≤ 0.12	≤ 0.12	97.2	
E. coli (182)																						
SPR206		15	8.2	134	81.9	30	98.4	1	98.9	1	99.5	0	99.5	1	100.0			0.06	0.12			
Colistin					39	21.4	135	74.2	7	95.6	0	95.5	0	95.5	1	96.0			0.25	0.25	99.5	
Polymyxin-B					56	30.8	114	62.7	8	93.4	3	97.8	3	99.5	1	100.0			0.25	0.25		
Ceftriaxone					143	78.6	3	80.2	0	80.2	1	80.8	0	80.8	0	81.9	33	100.0	≤ 0.12	>8	80.8	
Meropenem					182	100.0												≤ 0.12	≤ 0.12	100.0		
K. pneumoniae (181)																						
SPR206		9	5.0	146	85.6	19	96.1	4	98.3	0	98.3	0	98.3	0	98.3	2	99.4	1	100.0	0.06	0.12	
Colistin					85	47.0	90	50.3	2	97.8	1	98.3	0	98.3	0	98.3	2	99.4	0.25	0.25	98.3	
Polymyxin-B					60	33.1	108	59.7	7	92.8	2	97.8	1	98.3	1	99.4	1	100.0	0.25	0.25		
Ceftriaxone					122	67.4	8	71.8	3	73.5	1	74.0	1	74.6	2	75.7	44	100.0	≤ 0.12	>8	74.0	
Meropenem					166	91.7	1	92.3	0	92.3	0	92.8	0	92.8	0	92.8	13	100.0	≤ 0.12	≤ 0.12	92.8	
E. cloacae species complex (94)																						
SPR206		5	5.3	57	66.0	14	80.9	4	85.1	1	86.2	0	86.2	0	86.2	1	88.3	11	100.0	0.06	>16	
Colistin					41	43.6	37	83.0	2	85.1	0	85.1	0	86.2	0	86.2	2	89.4	0.25	0.25	64	86.2
Polymyxin-B					27	28.7	48	79.8	4	84.0	1	85.1	1	86.2	2	88.3	2	90.4	0.25	0.25	32	
Ceftriaxone					20	21.3	19	41.5	5	59.6	2	64.9	3	70.2	1	71.3	27	100.0	0.5	>8	64.9	
Meropenem					85	90.4	3	94.7	0	97.9	0	97.9	0	97.9	0	97.9	1	100.0	≤ 0.12	≤ 0.12	97.9	
E. aerogenes (22)																						
SPR206					12	54.5	7	86.4	1	90.9	0	95.5	0	95.5	0	95.5	1	100.0	0.06	0.25		

^a The intensity of shading is proportional to the number of tested isolates within each row that display the indicated MIC value.
^b Greater than the highest concentration tested.
^c Includes *Citrobacter freundii* species complex (4 isolates; 1 *bla*_{KPC-2}, 1 *bla*_{KPC-3}, 1 *bla*_{OXA-48}, and 1 *bla*_{VIM-1}), *E. cloacae* species complex (9 isolates; 1 *bla*_{KPC-2}, 2 *bla*_{KPC-3}, 1 *bla*_{KPC-4}, 3 *bla*_{NDM-1}, and 1 *bla*_{VIM-1}), *Escherichia coli* (9 isolates; 3 *bla*_{KPC-2}, 2 *bla*_{KPC-3}, 1 *bla*_{NDM-1}, 1 *bla*_{NDM-5}, and 1 *bla*_{OXA-232}), 1 *bla*_{NDM-7}, and 1 *bla*_{OXA-48}), *Klebsiella oxytoca* (1 isolate, *bla*_{KPC-2}), and *K. pneumoniae* (9 isolates; 1 *bla*_{KPC-2}, 3 *bla*_{KPC-3}, 2 *bla*_{NDM-1}, and 3 *bla*_{OXA-48}).