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

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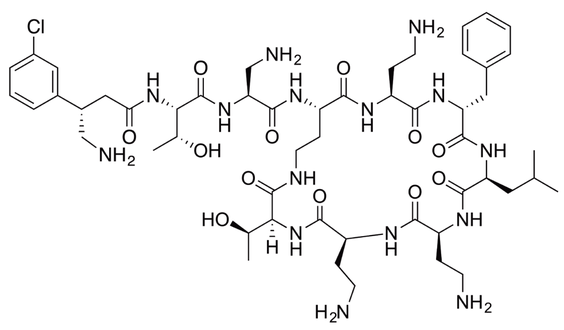
Introduction

- 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



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

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 MIC_{100} 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)

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

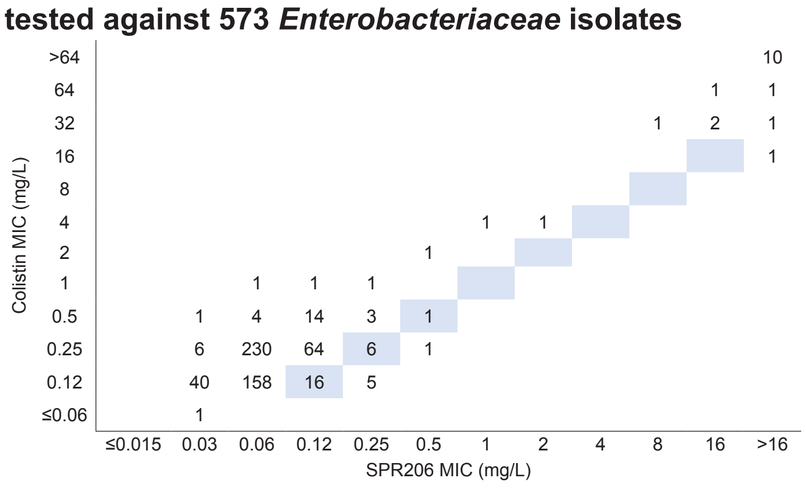

Figure 3 Comparison of polymyxin-B to SPR206 when tested against 573 *Enterobacteriaceae* isolates

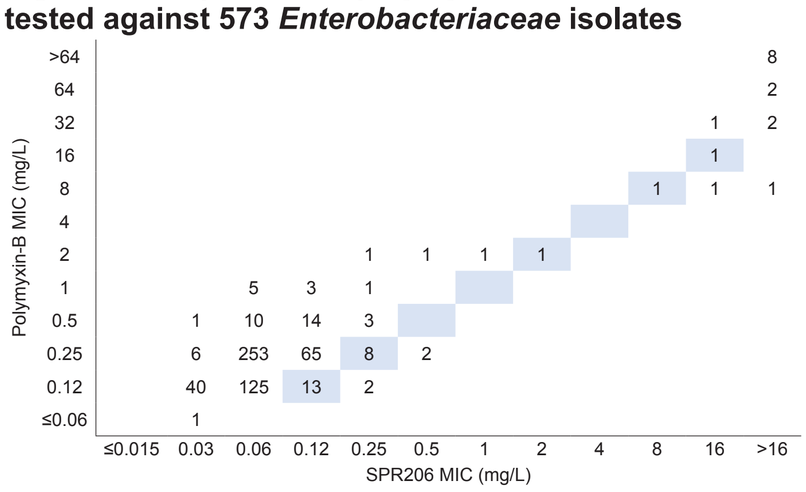

Table 1 Antimicrobial activity of SPR206 and comparators tested against the main organisms and organism groups

Organism group (no. of isolates) / Antimicrobial agent	No. and cumulative % of isolates at MIC (mg/L) of [a]: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	> [b]	MIC_{50}	MIC_{90}	EUCAST %S
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 96.9	1 97.0	3 97.6			13 100.0	0.06	0.12	
Colistin			1 0.2	206 38.3	293 92.4	18 95.7	3 96.3	1 96.5	2 96.9	0 96.9	1 97.0	4 97.8	2 98.2	10 100.0	0.25	0.25	96.5
Polymyxin-B			1 0.2	178 33.1	310 90.4	25 95.0	6 96.1	4 96.9	0 96.9	3 97.4	1 97.6	3 98.2	2 98.5	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 79.7				110 100.0	≤0.12	>8	77.4
Meropenem				516 95.4	6 96.5	3 97.0	0 97.0	1 97.2	0 97.2	1 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 95.6	7 99.5	0 99.5	0 99.5	1 100.0						0.25	0.25	99.5
Polymyxin-B				56 30.8	114 93.4	8 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 80.8	2 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	0 98.3	0 98.3	2 99.4			1 100.0	0.06	0.12	
Colistin				85 47.0	90 96.7	2 97.8	1 98.3	0 98.3	0 98.3	0 98.3	0 98.3	2 99.4	1 100.0		0.25	0.25	98.3
Polymyxin-B				60 33.1	108 92.8	7 96.7	2 97.8	1 98.3	0 98.3	1 98.9	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	0 74.6	2 75.7				44 100.0	≤0.12	>8	74.0
Meropenem				166 91.7	1 92.3	0 92.3	0 92.3	1 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	0 86.2	1 87.2	1 88.3			11 100.0	0.06	>16	
Colistin				41 43.6	37 83.0	2 85.1	0 85.1	1 86.2	0 86.2	0 86.2	1 87.2	2 89.4	1 90.4	9 100.0	0.25	64	86.2
Polymyxin-B				27 28.7	48 79.8	4 84.0	1 85.1	1 86.2	0 86.2	2 88.3	0 88.3	2 90.4	2 92.6	7 100.0	0.25	32	
Ceftriaxone				20 21.3	19 41.5	17 59.6	5 64.9	2 67.0	3 70.2	1 71.3				27 100.0	0.5	>8	64.9
Meropenem				85 90.4	4 94.7	3 97.9	0 97.9	0 97.9	0 97.9	1 98.9				1 100.0	≤0.12	≤0.12	97.9
E. aerogenes (22)																	
SPR206			12 54.5	7 86.4	1 90.9	1 95.5	0 95.5	0 95.5	0 95.5	0 95.5	0 95.5			1 100.0	0.06	0.25	

Organism group (no. of isolates) / Antimicrobial agent	No. and cumulative % of isolates at MIC (mg/L) of [a]: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	> [b]	MIC_{50}	MIC_{90}	EUCAST %S
E. aerogenes (22) *(continued)*																	
Colistin				8 36.4	11 86.4	2 95.5	0 95.5	0 95.5	0 95.5	0 95.5	0 95.5	0 95.5	0 95.5	1 100.0	0.25	0.5	95.5
Polymyxin-B				8 36.4	11 86.4	2 95.5	0 95.5	0 95.5	0 95.5	0 95.5	0 95.5	0 95.5	0 95.5	1 100.0	0.25	0.5	
Ceftriaxone				16 72.7	3 86.4	0 86.4	0 86.4	0 86.4	0 86.4	0 86.4				3 100.0	≤0.12	>8	86.4
Meropenem				21 95.5	1 100.0										≤0.12	≤0.12	100.0
K. oxytoca (19)																	
SPR206		6 31.6	12 94.7	1 100.0											0.06	0.06	
Colistin				17 89.5	2 100.0										0.12	0.25	100.0
Polymyxin-B				10 52.6	7 89.5	2 100.0									0.12	0.5	
Ceftriaxone				13 68.4	3 84.2	0 84.2	0 84.2	0 84.2	0 84.2	1 89.5				2 100.0	≤0.12	>8	84.2
Meropenem				19 100.0											≤0.12	≤0.12	100.0
Citrobacter spp. (19)																	
SPR206			6 31.6	11 89.5	2 100.0										0.12	0.25	
Colistin				6 31.6	11 89.5	2 100.0									0.25	0.5	100.0
Polymyxin-B				5 26.3	13 94.7	1 100.0									0.25	0.25	
Ceftriaxone				10 52.6	6 84.2	1 89.5	1 94.7	0 94.7	0 94.7	0 94.7				1 100.0	≤0.12	1	94.7
Meropenem				19 100.0											≤0.12	≤0.12	100.0
Carbapenem-resistant *Enterobacteriaceae* challenge set (32)[c]																	
SPR206		1 3.1	23 75.0	8 100.0											0.06	0.12	
Colistin				13 40.6	14 84.4	5 100.0									0.25	0.5	100.0
Polymyxin-B				2 6.2	24 81.2	3 90.6	3 100.0								0.25	0.5	
Ceftriaxone								1 3.1	0 3.1	1 6.2				30 100.0	>8	>8	0.0
Meropenem							1 3.1	2 9.4	7 31.2	4 43.8				18 100.0	>8	>8	9.4

[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}, 1 bla_{NDM-7}, 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} + $bla_{OXA-232}$, 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}).