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Introduction

- Non-fermentative gram-negative bacilli (NFGNB) are opportunistic organisms that have emerged as important healthcare-associated pathogens, mainly in the immunocompromised patient population
- These organisms are innately resistant to many antimicrobial classes due to the presence of intrinsic genes encoding β -lactamases and decreased permeability
- SPR206 is a polymyxin derivative compound being clinically developed for treating serious 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 a current collection of NFGNB

Materials and Methods

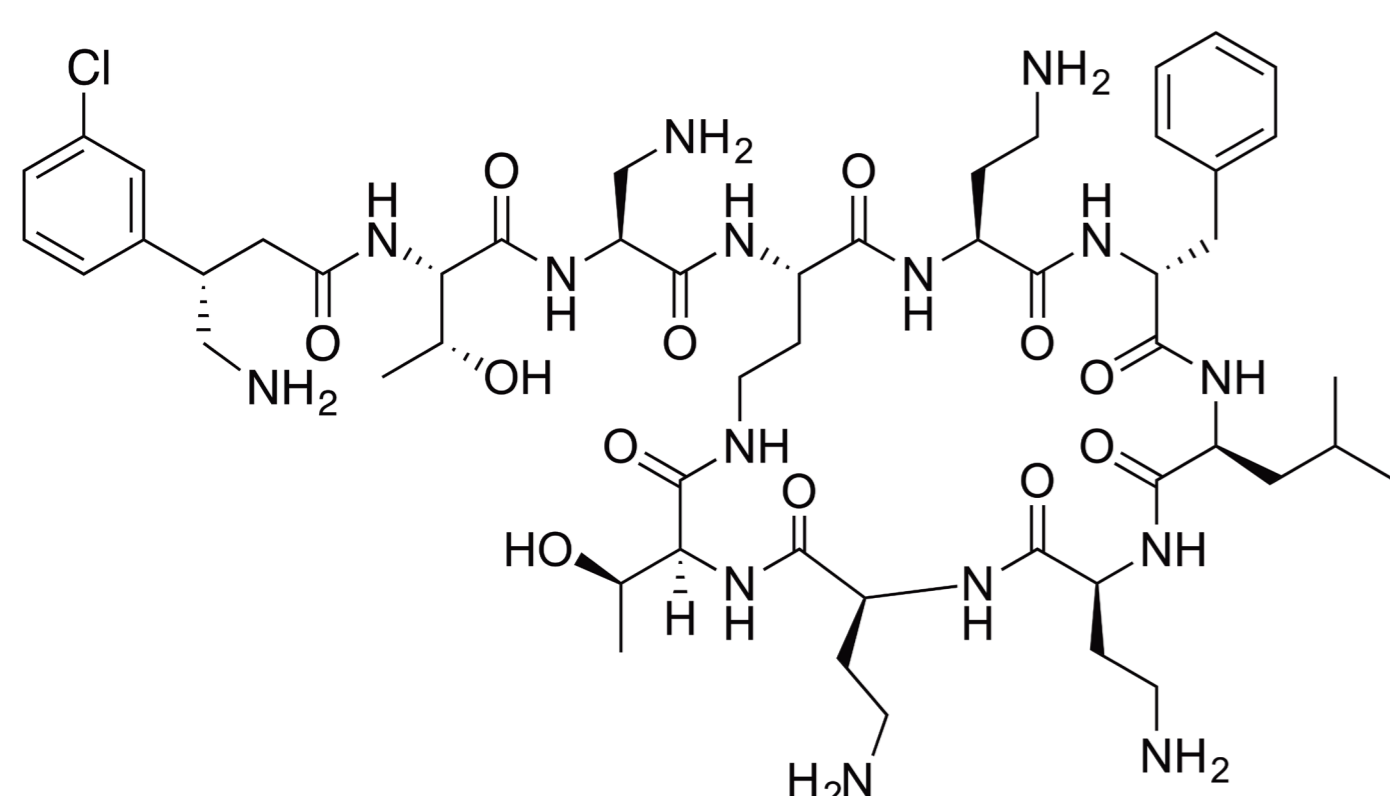
Bacterial isolates

- A total of 389 randomly selected isolates (182 *Pseudomonas aeruginosa*, 185 *Acinetobacter* spp., and 22 *Stenotrophomonas maltophilia*) representing current antimicrobial susceptibility profiles for the respective species were included
- In addition, a subset of 53 and 130 meropenem-nonsusceptible *P. aeruginosa* and *Acinetobacter* spp., respectively, were analyzed separately
- These isolates originated from the SENTRY Antimicrobial Surveillance Program (2016-2017) bank of organisms and were recovered from 37 medical centers in 20 European nations (n=163), 64 medical centers in the United States (n=203), 12 medical centers from 8 Asia-Pacific nations (n=32), and 12 medical centers from 8 Latin American nations (n=32)
- Isolates were collected from patients with pneumonia (55.4%), skin and skin structure infections (24.7%), bloodstream infections (12.8%), and other infections (7.2%)

Antimicrobial susceptibility testing

- Isolates were tested against SPR206 and select comparator agents for susceptibility by broth microdilution following guidelines in the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) document
- Frozen-form reference 96-well panels manufactured by JMI Laboratories were used for testing
- Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains (*Escherichia coli* ATCC 25922, *E. coli* NCTC 13846, *Klebsiella pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853)
- Breakpoint criteria for comparator agents were those available in the CLSI M100 (2018) document

Figure 1 Structure of SPR206



Results

- SPR206 inhibited all randomly selected *P. aeruginosa* at ≤ 2 mg/L and showed MIC results (MIC_{50/90}, 0.25/0.5 mg/L) 2-fold lower than colistin (MIC_{50/90}, 0.5/1 mg/L) and polymyxin B (MIC_{50/90}, 0.5/1 mg/L) (Table 1)
- Similar MIC results for the respective compounds were obtained against carbapenem-nonsusceptible *P. aeruginosa* compared with the randomly selected set (Table 2)
- Against *A. baumannii*, SPR206 (MIC_{50/90}, 0.12/0.25 mg/L) was 2- to 8- fold more potent than polymyxin-B (MIC_{50/90}, 0.25/1-2 mg/L) and 4- to 32-fold more potent than colistin (MIC_{50/90}, 0.5/4-8 mg/L) (Tables 1 and 2)
- In addition, SPR206 inhibited 95.7% of randomly selected *Acinetobacter* spp. or 93.1% of all tested *Acinetobacter* spp. at ≤ 2 mg/L
- SPR206 (MIC_{50/90}, 0.25/4 mg/L) and polymyxin-B (MIC_{50/90}, 0.5/4 mg/L) showed similar MIC values against *S. maltophilia*, and these compounds had MIC results 4- to 16-fold lower than colistin (MIC_{50/90}, 4/16 mg/L) (Table 1)

Conclusions

- Overall, SPR206 showed potent *in vitro* activity against a current collection of NFGNB, and its potency was consistently greater than the clinically available in-class comparator agents
- The *in vitro* results obtained for SPR206 warrant additional investigations to explore its clinical utility for treating infections caused by commonly multidrug-resistant gram-negative pathogens

Table 1 Antimicrobial activity of SPR206 and comparators tested against a random selection of non-fermentative gram-negative bacilli

Organism (no. of isolates)	Antimicrobial agent	Number and cumulative % of isolates inhibited at MIC (mg/L) of ^a :												MIC ₅₀	MIC ₉₀	%S ^c		
		≤ 0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32				64	> ^b
<i>P. aeruginosa</i> (182)																		
	SPR206		1	19	113	43	5	1									0.25	0.5
			0.5	11.0	73.1	96.7	99.5	100.0										
	Colistin				15	82	80	3	2								0.5	1
					8.2	53.3	97.3	98.9	100.0									98.9
	Polymyxin-B				22	139	20	1									0.5	1
					12.1	88.5	99.5	100.0										100.0
	Meropenem			25	36	35	28	17	8	12						21	0.5	>8
				13.7	33.5	52.7	68.1	77.5	81.9	88.5					100.0			77.5
<i>Acinetobacter</i> spp. (185)																		
	SPR206			53	90	25	8	1	0	1	1					6	0.12	0.25
				28.6	77.3	90.8	95.1	95.7	95.7	95.7	96.2	96.8				100.0		
	Colistin					38	78	40	8	4	3	3	1			6	0.5	4
						20.5	62.7	84.3	88.6	90.8	93.0	94.6	96.2	96.8	100.0			88.6
	Polymyxin-B				9	91	35	32	6	2	4	2	3	0		1	0.25	1
					4.9	54.1	73.0	90.3	93.5	94.6	96.8	97.8	99.5	99.5	100.0			93.5
	Meropenem			1	25	21	11	7	3	4						113	>8	>8
				0.5	14.1	25.4	31.4	35.1	36.8	38.9					100.0			35.1
<i>S. maltophilia</i> (22)																		
	SPR206		1	8	4	1	1	1	4	1	1						0.25	4
			4.5	40.9	59.1	63.6	68.2	72.7	90.9	95.5	100.0							
	Colistin			1	0	3	2	4	2	4	4	2					4	16
				4.5	4.5	18.2	27.3	45.5	54.5	72.7	90.9	100.0						
	Polymyxin-B			2	6	5	1	4	3	1							0.5	4
				9.1	36.4	59.1	63.6	81.8	95.5	100.0								
	Meropenem															22	>8	>8
															100.0			

^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 Susceptible breakpoints were those from CLSI/EUCAST (2018).

Table 2 Antimicrobial activity of SPR206 and comparators tested against meropenem-nonsusceptible non-fermentative gram-negative bacilli

Organism (no. of isolates)	Antimicrobial agent	Number and cumulative % of isolates inhibited at MIC (mg/L) of ^a :												MIC ₅₀	MIC ₉₀	%S ^c		
		≤ 0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32				64	> ^b
<i>P. aeruginosa</i> (53)																		
	SPR206			5	25	19	3	1									0.25	0.5
				9.4	56.6	92.5	98.1	100.0										
	Colistin				3	27	22	0	0	1							0.5	1
					5.7	56.6	98.1	98.1	98.1	100.0								98.1
	Polymyxin-B				8	35	9	1									0.5	1
					15.1	81.1	98.1	100.0										100.0
<i>Acinetobacter</i> spp. (130)																		
	SPR206			40	64	13	4	1	0	0	1	1				6	0.12	0.25
				30.8	80.0	90.0	93.1	93.8	93.8	93.8	94.6	95.4				100.0		
	Colistin					22	54	27	6	4	3	3	1			6	0.5	8
						16.9	58.5	79.2	83.8	86.9	90.0	92.3	94.6	95.4	100.0			83.8
	Polymyxin-B				4	61	22	25	6	2	4	2	3	0		1	0.25	2
					3.1	50.0	66.9	86.2	90.8	92.3	95.4	96.9	99.2	99.2	100.0			90.8

^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 Susceptible breakpoints were those from CLSI/EUCAST (2018).

Acknowledgements

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