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In Vitro Activity of SPR206 and Comparator Compounds against Enterobacterales Isolates Responsible for Infections in Hospitals in Europe and Adjacent Regions

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Introduction

- The proportion of isolates producing extended-spectrum β-lactamases (ESBLs) has increased in both hospital and nosocomial settings worldwide.
  - This increased frequency challenges empiric treatment of serious infections and may promote the use of more potent antimicrobial agents, such as carbapenems.
- This scenario helped potentialize the emergence and dissemination of Gram-negative multidrug-resistant (MDR) pathogens in recent decades, including carbapenem-resistant Enterobacterales, for which treatment options are often limited.
- SPR206 is a next-generation polymyxin under clinical development to treat pneumonia, bloodstream, and urinary tract infections caused by Gram-negative MDR pathogens.
- The *in vitro* activity of SPR206 and comparators was monitored against Gram-negative pathogens causing infection in European hospitals during 2021 as part of the SENTRY Antimicrobial Surveillance Program.
- We report the activity of SPR206 and comparators against Enterobacterales from European countries and adjacent regions.

Materials and Methods

Bacterial organisms

- A total of 1,614 Enterobacterales were collected from 35 medical centres in 16 countries in Europe plus Israel and Turkey, as part of the SENTRY Antimicrobial Surveillance Program in 2021.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) guidelines.
- Frozen-form broth microdilution panels were manufactured by JMI Laboratories (North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth per the CLSI guidelines.
- Quality assurance was performed by sterility checks, colony counts, and testing CLSI-recommended quality control reference strains.
- MIC interpretations were performed using European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for comparators.
- Clinical breakpoints are not available for SPR206, so values throughout indicate the percentage of isolates inhibited by SPR206 at ≤2 mg/L for comparison purposes only.

Resistant subset definitions

- ESBL producers were presumptively defined as *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* with ceftriaxone, ceftazidime, or aztreonam MICs ≥2 mg/L.
- MDR was defined as any isolate resistant to ≥3 classes of antibiotics.

Results

- *E. coli* (425 isolates) and *K. pneumoniae* (425) were the most common pathogens, followed by *Enterobacter cloacae* species complex (213), *Citrobacter* spp. (121), *K. oxytoca* (110), *Serratia marcescens* (106), *K. aerogenes* (65), *P. mirabilis* (60), *Morganella morganii* (60), and 8 other species/groups (29) (data not shown).
- Overall, SPR206 and colistin had MIC_{50} results of 0.06 mg/L and 0.25 mg/L against Enterobacterales, respectively, excluding those isolates intrinsically resistant to polymyxins (Tables 1 and 2).
  - Indole-positive Proteeae, *Proteus* spp., and *Serratia* spp., which are intrinsically resistant to polymyxins (MIC, >8 mg/L), had elevated SPR206 MICs of >8 mg/L (data not shown).
  - Excluding these organisms, SPR206 ($MIC_{50/90}$, 0.06/0.25 mg/L) and meropenem ($MIC_{50/90}$, 0.03/0.06 mg/L) showed the lowest MICs against this subset, followed by colistin ($MIC_{50/90}$, 0.25/0.5 mg/L) and ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.5 mg/L) (Table 2).
- In general, *E. coli* isolates were susceptible to various agents tested, such as colistin (99.8% susceptible), ceftazidime-avibactam (100% susceptible), piperacillin-tazobactam (90.6% susceptible), ceftolozane-tazobactam (99.1% susceptible), and the carbapenems (100% susceptible) (Table 2).
  - However, 21.6% were classified to presumptively produce ESBL enzymes, which was reflected in decreased susceptibilities to ceftazidime (21.6% non-susceptible), ceftriaxone (20.7% non-susceptible), and aztreonam (21.6% non-susceptible).
- SPR206 ($MIC_{50/90}$, 0.06/0.25 mg/L) had MICs 2- to 4-fold lower than colistin ($MIC_{50/90}$, 0.25/0.5 mg/L) against *K. pneumoniae* (Table 2).
  - Colistin (92.9% susceptible) and ceftazidime-avibactam (98.6% susceptible) were active against *K. pneumoniae* (Table 2).
- MDR Enterobacterales collected from Eastern Europe showed resistance rates between 26.4% and 98.9%, except for ceftazidime-avibactam, which was active against 91.2% of these isolates (Table 2).
- SPR206 ($MIC_{50/90}$, 0.06/0.12 mg/L) had the lowest MIC_{50} and MIC_{90} values and showed MICs 2- to 4-fold lower than colistin ($MIC_{50/90}$, 0.25/0.25 mg/L) against MDR isolates from Western Europe (Table 2).

Conclusions

- SPR206 was consistently more potent than colistin against Enterobacterales pathogens in Europe and its adjacent regions.
  - SPR206 inhibited 95.3% of those Enterobacterales not intrinsically resistant to polymyxins at MIC results of ≤2 mg/L.
- SPR206 remained active against MDR isolates, where limited intravenous options were available.
- These *in vitro* SPR206 data, combined with its favorable safety and tolerability profiles in Phase 1 studies, support the continued clinical advancement and development of SPR206.

Table 1. MIC distributions of SPR206 obtained against Enterobacterales and resistant subsets

Organism/Group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:													MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64		
All Enterobacterales (1,614)	239 (14.8)	688 (57.4)	264 (73.8)	79 (78.7)	22 (80.0)	9 (80.6)	4 (80.9)	1 (80.9)	5 (81.2)	15 (82.2)	12 (82.9)	10 (83.5)	266 (100)	0.06	>64
Enterobacterales (1,368)[a]	239 (17.5)	688 (67.8)	263 (87.0)	79 (92.8)	22 (94.4)	9 (95.0)	4 (95.3)	1 (95.4)	5 (95.8)	12 (96.6)	12 (97.5)	8 (98.1)	26 (100)	0.06	0.25
E. coli (425)	91 (21.4)	262 (83.1)	61 (97.4)	8 (99.3)	0 (99.3)	0 (99.3)	2 (99.8)	1 (100.0)						0.06	0.12
K. pneumoniae (425)	45 (10.6)	197 (56.9)	122 (85.6)	23 (91.1)	5 (92.2)	3 (92.9)	1 (93.2)	0 (93.2)	3 (93.9)	10 (96.2)	7 (97.9)	4 (98.8)	5 (100)	0.06	0.25
MDR Eastern EU (91)[a, b]	7 (7.7)	32 (42.9)	17 (61.5)	6 (68.1)	2 (70.3)	2 (72.5)	1 (73.6)	0 (73.6)	1 (74.7)	7 (82.4)	7 (90.1)	6 (96.7)	3 (100)	0.12	32
MDR Western EU (88)[a, c]	15 (17.0)	50 (73.9)	15 (90.9)	4 (95.5)	1 (96.6)	0 (96.6)	0 (96.6)	0 (96.6)	1 (97.7)	2 (100.0)				0.06	0.12

[a] Excludes intrinsically resistant isolates, such as *Morganella* spp., *Proteus* spp., *Providencia* spp., and *Serratia* spp.
[b] Includes *Citrobacter freundii* species complex (1), *Enterobacter cloacae* species complex (9), *Escherichia coli* (16), *Klebsiella oxytoca* (3), and *K. pneumoniae* (62).
[c] Includes *C. freundii* species complex (1), *E. cloacae* species complex (6), *E. coli* (17), *K. aerogenes* (1), *K. oxytoca* (5), *K. pneumoniae* (57), and *K. variicola* (1).

Table 2. Antimicrobial activity of SPR206 and comparators against Enterobacterales and resistant subsets

Antimicrobial agent	MIC (mg/L)			EUCAST[a]		
	50%	90%	Range	%S	%I	%R
Enterobacterales (1,368)[a]						
SPR206[a]	0.06	0.25	≤0.03 to >64	95.3		
Colistin	0.25	0.5	≤0.06 to >8	95.2		4.8
Aztreonam	0.12	>16	≤0.03 to >16	69.8	1.6	28.6
Meropenem	0.03	0.06	≤0.015 to >32	95.9	0.8	3.3
Imipenem	≤0.12	1	≤0.12 to >8	96.1	0.7	3.3
Ceftazidime	0.25	>32	0.03 to >32	69.5	4.2	26.2
Ceftazidime-avibactam	0.12	0.5	≤0.015 to >32	99.3		0.7
Ceftriaxone	0.12	>8	≤0.06 to >8	70.0	0.7	29.3
Piperacillin-tazobactam	2	128	≤0.06 to >128	76.2		23.8
Amikacin	2	4	≤0.25 to >32	95.4		4.6
Tobramycin	0.5	16	≤0.12 to >16	84.8		15.2
Tigecycline	0.25	0.5	≤0.06 to >8			
Levofloxacin	0.06	16	≤0.015 to >32	78.2	4.1	17.7
Trimethoprim-sulfamethoxazole	≤0.12	>4	≤0.12 to >4	74.7	0.4	24.8
Ceftolozane-tazobactam	0.25	8	≤0.12 to >16	86.5		13.5
E. coli (425)						
SPR206[a]	0.06	0.12	≤0.03 to 4	99.8		
Colistin	0.25	0.25	0.12 to 4	99.8		0.2
Aztreonam	0.12	>16	≤0.03 to >16	78.4	1.6	20.0
Meropenem	≤0.015	0.03	≤0.015 to 0.25	100.0	0.0	0.0
Imipenem	≤0.12	≤0.12	≤0.12 to 1	100.0	0.0	0.0
Ceftazidime	0.25	16	0.03 to >32	78.4	6.1	15.5
Ceftazidime-avibactam	0.12	0.25	≤0.015 to 2	100.0		0.0
Ceftriaxone	≤0.06	>8	≤0.06 to >8	79.3	0.2	20.5
Piperacillin-tazobactam	2	8	≤0.06 to >128	90.6		9.4
Amikacin	4	8	1 to >32	96.5		3.5
Tobramycin	1	8	0.25 to >16	86.4		13.6
Tigecycline	0.12	0.25	≤0.06 to 2	99.1		0.9
Levofloxacin	0.06	16	≤0.015 to >32	71.5	1.4	27.1
Trimethoprim-sulfamethoxazole	≤0.12	>4	≤0.12 to >4	66.2	0.5	33.3
Ceftolozane-tazobactam	0.25	0.5	≤0.12 to >16	99.1		0.9
K. pneumoniae (425)						
SPR206[a]	0.06	0.25	≤0.03 to >64	93.2		
Colistin	0.25	0.5	0.12 to >8	92.9		7.1
Aztreonam	0.12	>16	≤0.03 to >16	60.5	1.2	38.4
Meropenem	0.03	8	≤0.015 to >32	87.8	2.4	9.9
Imipenem	≤0.12	4	≤0.12 to >8	88.7	1.4	9.9
Ceftazidime	0.5	>32	0.06 to >32	58.6	3.1	38.4
Ceftazidime-avibactam	0.12	1	≤0.015 to >32	98.6		1.4
Ceftriaxone	≤0.06	>8	≤0.06 to >8	60.2	0.7	39.1
Piperacillin-tazobactam	4	>128	0.25 to >128	66.4		33.6
Amikacin	2	16	0.5 to >32	89.9		10.1
Tobramycin	0.5	>16	0.25 to >16	70.8		29.2
Tigecycline	0.5	1	0.12 to >8			
Levofloxacin	0.06	32	≤0.015 to >32	66.1	8.7	25.2
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12 to >4	62.3	0.7	37.0
Ceftolozane-tazobactam	0.5	>16	≤0.12 to >16	81.2		18.8
MDR Eastern (91)[b]						
SPR206[a]	0.12	32	≤0.03 to >64	73.6		
Colistin	0.25	>8	0.12 to >8	73.6		26.4
Aztreonam	>16	>16	0.5 to >16	2.2	0.0	97.8
Meropenem	0.06	>32	≤0.015 to >32	59.3	5.5	35.2
Imipenem	0.25	>8	≤0.12 to >8	61.5	5.5	33.0
Ceftazidime	>32	>32	1 to >32	1.1	1.1	97.8
Ceftazidime-avibactam	0.5	2	0.03 to >32	91.2		8.8
Ceftriaxone	>8	>8	0.5 to >8	1.1	0.0	98.9
Piperacillin-tazobactam	>128	>128	2 to >128	13.2		86.8
Amikacin	8	>32	1 to >32	59.3		40.7
Tobramycin	>16	>16	0.25 to >16	8.8		91.2
Tigecycline	0.5	2	0.12 to 8			
Levofloxacin	16	>32	0.5 to >32	2.2	13.2	84.6
Trimethoprim-sulfamethoxazole	>4	>4	≤0.12 to >4	13.2	2.2	84.6
Ceftolozane-tazobactam	16	>16	0.25 to >16	36.3		63.7
MDR Western (88)[b]						
SPR206[a]	0.06	0.12	≤0.03 to 16	96.6		
Colistin	0.25	0.25	0.12 to >8	95.5		4.5
Aztreonam	>16	>16	0.25 to >16	2.3	2.3	95.5
Meropenem	0.06	>32	≤0.015 to >32	78.4	6.8	14.8
Imipenem	≤0.12	>8	≤0.12 to >8	80.7	2.3	17.0
Ceftazidime	>32	>32	0.25 to >32	3.4	4.5	92.0
Ceftazidime-avibactam	0.25	2	≤0.015 to >32	97.7		2.3
Ceftriaxone	>8	>8	≤0.06 to >8	4.5	1.1	94.3
Piperacillin-tazobactam	64	>128	4 to >128	15.9		84.1
Amikacin	4	32	0.5 to >32	76.1		23.9
Tobramycin	16	>16	0.25 to >16	12.5		87.5
Tigecycline	0.5	2	0.12 to >8			
Levofloxacin	16	>32	0.06 to >32	10.2	10.2	79.5
Trimethoprim-sulfamethoxazole	>4	>4	≤0.12 to >4	22.7	0.0	77.3
Ceftolozane-tazobactam	2	>16	≤0.12 to >16	52.3		47.7

[a] Criteria as published by EUCAST (2022); excludes intrinsically resistant isolates, such as *Morganella* spp., *Proteus* spp., *Providencia* spp., and *Serratia* spp.; Clinical breakpoints are not available for SPR206, so values indicate the percentage of isolates inhibited by SPR206 at ≤2 mg/L for comparison purposes only.
[b] See footnotes on Table 1 for additional information.

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