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 pathogens (Figure 1).
- This study evaluated the in vitro potency of SPR206 and compared its potency to those of carbapenems 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 resistant to 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 52 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 performed 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-foam reference 96-well plates manufactured by JMI Laboratories were used in testing.
- Breakpoint criteria for comparator agents were from the CLSI M100 (2018) and EUCAST (2018) documents.

Results

- SPR206 (MIC<sub>90</sub> 0.006/0.12 mg/L) was more potent than colistin and polymyxin B (MIC<sub>90</sub> 0.25/0.25 mg/L).
- SPR206 showed 93.2% of all Enterobacteriaceae at ≤0.12 mg/L, while colistin and polymyxin B inhibited 38.3% and 35.7%, respectively, at ≤0.12 mg/L (Table 1).
- SPR206 had an MIC<sub>50</sub> of 52 mg/L against Enterococcus, Citrobacter, Salmonella, and Shigella species (Table 1).
- Ceftriaxone displayed a broad spectrum of activity against CRE isolates (MIC ≤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 active (MIC ≤0.12≤0.5 mg/L) against these isolates and 97.9% were susceptible at the CLSI/EUCAST breakpoints of ≤1 mg/L.
- SPR206 showed increased MIC values for strains isolated from infections (9%).

Conclusions

- Overall, SPR206 was highly potent against a contemporary collection of Enterobacteriaceae isolates.
- Based on MIC<sub>90</sub> 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 groups

<table>
<thead>
<tr>
<th>Organism group (no. of isolates)</th>
<th>No. and cumulative % of isolates at MIC (μg/mL) of SPR206 (MIC&lt;sub&gt;90&lt;/sub&gt;)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;25&lt;/sub&gt;</th>
<th>EUCAST&lt;sup&gt;5&lt;/sup&gt; %&lt;sup&gt;5&lt;/sup&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;25&lt;/sub&gt;</th>
<th>EUCAST&lt;sup&gt;5&lt;/sup&gt; %&lt;sup&gt;5&lt;/sup&gt;</th>
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<td></td>
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<td></td>
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<tr>
<td>Colistin</td>
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<td>0.5</td>
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<td>96.4</td>
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<tr>
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<td>0.12</td>
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<td>0.5</td>
<td>0.25</td>
<td>0.12</td>
<td>96.4</td>
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<tr>
<td>Ceftriaxone</td>
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<td>0.03</td>
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<td>0.12</td>
<td>0.06</td>
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<td>Meropenem</td>
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<td>0.12</td>
<td>96.4</td>
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</tbody>
</table>

References


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

Figure 4 Comparison of carbapenems to SPR206 when tested against 573 Enterobacteriaceae isolates

*The intensity of shading is proportional to the number of isolates within each MIC range that display the indicated MIC value.

- Greater than the highest concentration tested.
- OXA-48 carbapenem-resistant Enterobacteriaceae (CRE) isolates: 1 bla<sup>b</sup>-OXA-48, 1 bla<sup>b</sup>-OXA-48, 1 bla<sup>b</sup>-OXA-48, and 1 bla<sup>b</sup>-OXA-48.
- CRE: carbapenem-resistant Enterobacteriaceae (CRE) isolates: 1 bla<sup>b</sup>-OXA-48, 1 bla<sup>b</sup>-OXA-48, 1 bla<sup>b</sup>-OXA-48, and 1 bla<sup>b</sup>-OXA-48.