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In Vitro Activity of SPR741 Combined with Three Novel Compounds Against Recent Clinical Isolates of *Acinetobacter baumannii* and Enterobacteriaceae

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Abstract

Background: SPR741 is a potentiator compound currently under development by Spero Therapeutics. The objective of the present study was to investigate the *in vitro* activity of SPR741 in combination with three novel compounds, SPR719, SPR750, and SPR751, against 400 recent clinical isolates.

Methods: Minimal inhibitory concentrations (MICs) were determined following CLSI microdilution guidelines against a global collection of 100 *Acinetobacter baumannii*, 100 *Enterobacter cloacae*, 100 *Escherichia coli* and 100 *Klebsiella pneumoniae* from 2014-2015. Compounds tested included SPR719, SPR750, and SPR751 alone and in combination with SPR741 at fixed concentrations of 2 and 8 µg/mL.

Results: Addition of fixed concentrations of SPR741 at both 2 and 8 µg/mL reduced the MIC values of SPR719, SPR750, and SPR751, with the greatest effect seen at a concentration of 8 µg/mL. Results for the addition of SPR741 at 8 µg/mL are shown in the Table. SPR719 was the most active of the three compounds in combination with SPR741, with a reduction in MIC_{90} values of at least 16-fold for *A. baumannii* and at least 128-fold for the Enterobacteriaceae, followed by SPR751 (at least 16-fold for *A. baumannii* and at least 64-fold for the Enterobacteriaceae) and SPR750 (at least 4-fold for *A. baumannii* and at least 8-fold for the Enterobacteriaceae). SPR719, SPR750, and SPR751 had limited activity on their own.

***In vitro* activity of SPR719, SPR750, and SPR751 alone and in combination with SPR741**

Compound	MIC$_{50/90}$ (µg/mL) *A. baumannii*	*E. cloacae*	*E. coli*	*K. pneumoniae*
SPR719	16/>16	>16/>16	8/16	16/>16
SPR719 + SPR741 @ 8 µg/mL	0.25/2	≤0.03/0.12	≤0.03/≤0.03	0.06/0.25
SPR750	>16/>16	>16/>16	>16/>16	>16/>16
SPR750 + SPR741 @ 8 µg/mL	0.5/8	0.06/0.5	0.06/0.12	0.5/2
SPR751	>16/>16	>16/>16	>16/>16	>16/>16
SPR751 + SPR741 @ 8 µg/mL	0.25/2	≤0.03/0.25	≤0.03/0.06	0.12/0.5

Conclusions: SPR741 exhibited strong potential for increasing the *in vitro* activity of SPR719, SPR750, and SPR751 against *A. baumannii, E. cloacae, E. coli and K. pneumoniae*. Further development of this potentiator compound could provide a valuable therapeutic option for treating infections caused by resistant gram-negative bacilli.

Introduction

SPR741 is a potentiator compound currently under development by Spero Therapeutics. SPR741 interacts with the outer membrane of Gram-negative bacteria to increase permeability and allow Gram-positive antibiotics to enter and be delivered to their targets. The objective of the present study was to investigate the *in vitro* activity of SPR741 in combination with three novel compounds, SPR719, SPR750, and SPR751, against 400 recent clinical isolates.

Materials & Methods

- MICs were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [1] against a global collection of 100 *Acinetobacter baumannii*, 100 *Enterobacter cloacae*, 100 *Escherichia coli* and 100 *Klebsiella pneumoniae* from 2014-2015.
- SPR719, SPR750, and SPR751were tested alone, and in combination with SPR741 at fixed concentrations of 2, and 8 µg/mL.

Results

Table 1. *In vitro* activity of SPR741 in combination with SPR719, SPR750, and SPR751*

Organism (N)	Compound	MIC_{50}	MIC_{90}	Range
Acinetobacter baumannii (100)	SPR719	16	> 16	0.12 - > 16
	SPR719 + SPR741 AT 2 µg/mL	1	4	≤0.03 - > 16
	SPR719 + SPR741 AT 8 µg/mL	0.25	2	≤0.03 - 16
	SPR750	> 16	> 16	0.5 - > 16
	SPR750 + SPR741 AT 2 µg/mL	16	> 16	≤0.03 - > 16
	SPR750 + SPR741 AT 8 µg/mL	0.5	8	≤0.03 - > 16
	SPR751	> 16	> 16	0.12 - > 16
	SPR751 + SPR741 AT 2 µg/mL	2	8	≤0.03 - > 16
	SPR751 + SPR741 AT 8 µg/mL	0.25	2	≤0.03 - > 16
Enterobacter cloacae (100)	SPR719	> 16	> 16	2 - > 16
	SPR719 + SPR741 AT 2 µg/mL	1	4	0.25 - 8
	SPR719 + SPR741 AT 8 µg/mL	≤0.03	0.12	≤0.03 - 0.5
	SPR750	> 16	> 16	> 16 - > 16
	SPR750 + SPR741 AT 2 µg/mL	> 16	> 16	2 - > 16
	SPR750 + SPR741 AT 8 µg/mL	0.06	0.5	≤0.03 - 4
	SPR751	> 16	> 16	> 16 - > 16
	SPR751 + SPR741 AT 2 µg/mL	4	> 16	0.25 - > 16
	SPR751 + SPR741 AT 8 µg/mL	≤0.03	0.25	≤0.03 - 0.5
Escherichia coli (100)	SPR719	8	16	0.06 - > 16
	SPR719 + SPR741 AT 2 µg/mL	0.5	1	≤0.03 - 2
	SPR719 + SPR741 AT 8 µg/mL	≤0.03	≤0.03	≤0.03 - 0.06
	SPR750	> 16	> 16	1 - > 16
	SPR750 + SPR741 AT 2 µg/mL	8	> 16	0.12 - > 16
	SPR750 + SPR741 AT 8 µg/mL	0.06	0.12	≤0.03 - 0.5
	SPR751	> 16	> 16	0.25 - > 16
	SPR751 + SPR741 AT 2 µg/mL	1	4	≤0.03 - > 16
	SPR751 + SPR741 AT 8 µg/mL	≤0.03	0.06	≤0.03 - 0.25
Klebsiella pneumoniae (100)	SPR719	16	> 16	2 - > 16
	SPR719 + SPR741 AT 2 µg/mL	4	8	0.5 - > 16
	SPR719 + SPR741 AT 8 µg/mL	0.06	0.25	≤0.03 - 16
	SPR750	> 16	> 16	> 16 - > 16
	SPR750 + SPR741 AT 2 µg/mL	> 16	> 16	16 - > 16
	SPR750 + SPR741 AT 8 µg/mL	0.5	2	≤0.03 - > 16
	SPR751	> 16	> 16	> 16 - > 16
	SPR751 + SPR741 AT 2 µg/mL	> 16	> 16	1 - > 16
	SPR751 + SPR741 AT 8 µg/mL	0.12	0.5	≤0.03 - > 16

*MIC_{50}, MIC_{90}, and range in µg/mL

Figure 1a. MIC distribution of SPR719 alone and in combination with SPR741 at 8 µg/mL for 100 *Acinetobacter baumannii.*

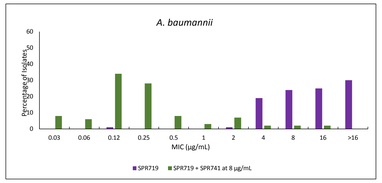


Figure 1b. MIC distribution of SPR719 alone and in combination with SPR741 at 8 µg/mL for 100 *Enterobacter cloacae.*

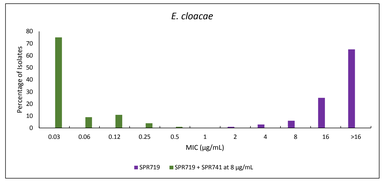


Figure 1c. MIC distribution of SPR719 alone and in combination with SPR741 at 8 µg/mL for 100 *Escherichia coli.*

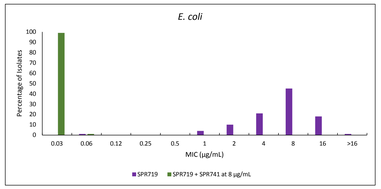


Figure 1d. MIC distribution of SPR719 alone and in combination with SPR741 at 8 µg/mL for 100 *Klebsiella pneumoniae.*

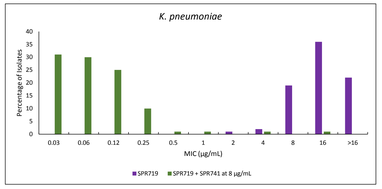


Figure 2a. MIC distribution of SPR750 alone and in combination with SPR741 at 8 µg/mL for 100 *Acinetobacter baumannii.*

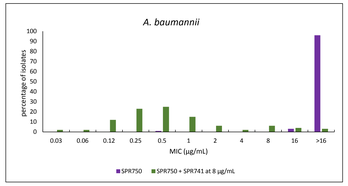


Figure 2b. MIC distribution of SPR750 alone and in combination with SPR741 at 8 µg/mL for 100 *Enterobacter cloacae.*

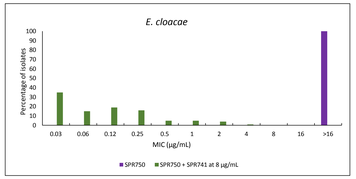


Figure 2c. MIC distribution of SPR750 alone and in combination with SPR741 at 8 µg/mL for 100 *Escherichia coli.*

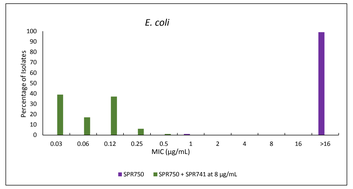


Figure 2d. MIC distribution of SPR750 alone and in combination with SPR741 at 8 µg/mL for 100 *Klebsiella pneumoniae.*

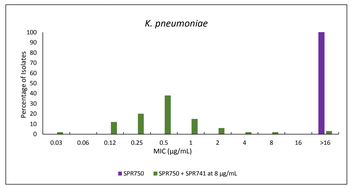


Figure 3a. MIC distribution of SPR751 alone and in combination with SPR741 at 8 µg/mL for 100 *Acinetobacter baumannii.*

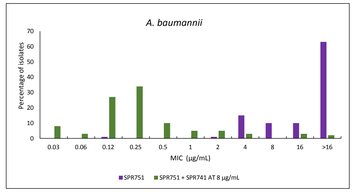


Figure 3b. MIC distribution of SPR751 alone and in combination with SPR741 at 8 µg/mL for 100 *Enterobacter cloacae.*

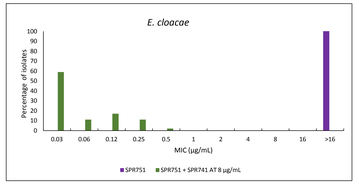


Figure 3c. MIC distribution of SPR751 alone and in combination with SPR741 at 8 µg/mL for 100 *Escherichia coli*

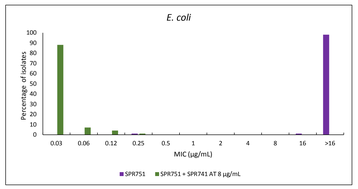
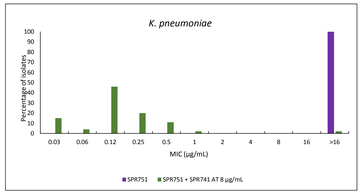


Figure 3d. MIC distribution of SPR751 alone and in combination with SPR741 at 8 µg/mL for 100 *Klebsiella pneumoniae*



Conclusions

- **SPR741 exhibited strong potential for increasing the *in vitro* activity of SPR719, SPR750, and SPR751 against *A. baumannii, E. cloacae, E. coli and K. pneumoniae.***
- **Further development of this potentiator compound could provide a valuable therapeutic option for treating infections caused by resistant gram-negative bacilli.**

References

1. Clinical Laboratory Standards Institute. 2015. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Tenth Edition. CLSI document M07-A10 Wayne, PA.
2. Clinical and Laboratory Standards Institute. 2016. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-sixth Informational Supplement. CLSI Document M100S 2016. Wayne, PA.

Acknowledgements

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