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In vitro activity of a Novel Antibacterial Agent (RX-P873) Against Gram-negative Bacteria

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Revised Abstract

Background: The novel antibacterial agent RX-P873 is currently in early pre-clinical studies and has shown excellent *in vivo* activity in systemic and tissue-based infection models. The current study determined the activity of RX-P873 against a recent collection of Gram-negative bacteria.
Methods: RX-P873 was tested against Gram-negative bacteria, including 53 *Acinetobacter baumannii*, 31 *Enterobacter* spp., 56 *Escherichia coli*, 35 *Klebsiella pneumoniae* and 52 *Pseudomonas aeruginosa* isolated from patients in various world-wide locations during 2012-2013. MIC tests were performed by broth microdilution against all isolates in line with CLSI susceptibility testing standards (M07-A9).
Results: Cumulative percent MIC frequency distributions for RX-P873 are shown in the Figure [Fig. 2 in main poster].
Conclusions: RX-P873 showed excellent activity against all the Gram-negative bacterial species tested with narrow MIC distributions and MIC_{90} ranging from 0.25 – 4 µg/ml.

Introduction

The emergence and increasing prevalence of antimicrobial resistance in Gram-negative bacteria is currently severely compromising therapeutic options for caregivers. These especially include members of the *Enterobacteriaceae*, such as *Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp., (amongst others) and non-fermentor genera including *Acinetobacter* spp. and *Pseudomonas* spp. The novel antibacterial agent RX-P873 is currently in early pre-clinical studies and has shown excellent *in vivo* activity in systemic and tissue-based infection models (the structure of RX-P873 is shown in Figure 1). The current study determined the activity of RX-P873 against a recent collection of Gram-negative bacteria.

Materials & Methods

- A total of 227 isolates were tested comprising 53 *Acinetobacter baumannii*, 31 *Enterobacter* spp., 56 *Escherichia coli*, 35 *Klebsiella pneumoniae* and 52 *Pseudomonas aeruginosa* isolated from patients in various world-wide locations during 2012-2013.
- MIC tests were performed by broth microdilution according to CLSI susceptibility testing standards (1). CLSI breakpoints were used to evaluate susceptibility (2), with the exception of tigecycline where FDA breakpoints were used (3).
- Quality controls were performed on each day of testing using appropriate ATCC control strains, following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges (3).

Results

Figure 1: Chemical Structure of RX-P873

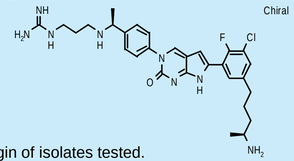


Table 1: Geographical origin of isolates tested.

Pathogen	Country:						Grand Total
	France	Germany	Italy	Russia	Spain	United States	
Acinetobacter baumannii	6	5	6	6	6	24	53
Enterobacter asburiae		1	1				2
Enterobacter cloacae	4	2	2	2	3	16	29
Escherichia coli	5	6	6	5	6	28	56
Klebsiella pneumoniae	4	3	4	3	3	18	35
Pseudomonas aeruginosa	6	6	5	6	6	23	52
Grand Total	25	23	24	22	24	109	227

Table 2. Summary MIC Data and Susceptibility for Antimicrobial Agents Against 56 *E. coli*.

Antimicrobial	CLSI Breakpoints (S|I|R)	MIC_{50}	MIC_{90}	%Sus	%Int	%Res	Min	Max
RX-P873	None available	0.25	0.25	-	-	-	0.06	0.5
Ciprofloxacin	≤0.06|0.12-0.5|≥1	0.015	>4	66.1	7.1	26.8	0.008	>4
Meropenem	≤1|2|≥4	0.015	0.03	100	0	0	0.015	0.06
Cefepime	≤2|4-8|≥16 [I=SDD]	0.06	32	85.7	1.8	12.5	0.015	>32
Ceftazidime	≤4|8|≥16	0.25	>32	87.5	0	12.5	0.06	>32
Piperacillin/tazobactam	≤16|32-64|≥128	2	32	89.3	7.1	3.6	1	128
Tigecycline	≤2|4|≥8 [FDA]	0.5	1	100	0	0	0.25	2
Tobramycin	≤4|8|≥16	0.5	16	85.7	1.8	12.5	≤0.25	>16
Colistin	None available	0.5	1	-	-	-	0.25	2

%Sus, %Int, %Res; % of isolates susceptible, intermediate or resistant, respectively. SDD, susceptible dose-dependent. Min; minimum MIC. Max; maximum MIC

Table 3. Summary MIC Data and Susceptibility for Antimicrobial Agents Against 53 *A. baumannii*

Antimicrobial	CLSI Breakpoints (S|I|R)	MIC_{50}	MIC_{90}	%Sus	%Int	%Res	Min	Max
RX-P873	None available	0.5	2	-	-	-	0.25	4
Ciprofloxacin	≤1|2|≥4	>64	>64	20.8	0	79.2	0.12	>64
Meropenem	≤2|4|≥8	32	>64	37.7	0	62.3	≤0.12	>64
Cefepime	≤8|16|≥32	64	>64	17.0	3.8	79.2	1	>64
Ceftazidime	≤8|16|≥32	>64	>64	17.0	1.9	81.1	2	>64
Piperacillin/tazobactam	≤16|32-64|≥128	>128	>128	17.0	1.9	81.1	≤0.25	>128
Tigecycline	None available	4	16	-	-	-	≤0.25	16
Tobramycin	≤4|8|≥16	8	>32	49.1	3.8	47.2	≤0.25	>32
Colistin	≤2|-|≥4	1	2	90.6	-	9.4	0.5	64

%Sus, %Int, %Res; % of isolates susceptible, intermediate or resistant, respectively. SDD, susceptible dose-dependent. Min; minimum MIC. Max; maximum MIC

Table 4. Summary MIC Data and Susceptibility for Antimicrobial Agents Against 52 *P. aeruginosa*

Antimicrobial	CLSI Breakpoints (S|I|R)	MIC50	MIC90	%Sus	%Int	%Res	Min	Max
RX-P873	None available	2	4	-	-	-	0.5	16
Ciprofloxacin	≤1|2|≥4	0.25	16	73.1	0	26.9	≤0.03	>64
Meropenem	≤2|4|≥8	0.5	64	65.4	3.8	30.8	≤0.12	64
Cefepime	≤8|16|≥32	4	16	76.9	13.5	9.6	0.06	64
Ceftazidime	≤8|16|≥32	2	32	78.8	3.8	17.3	0.06	>64
Piperacillin/tazobactam	≤16|32-64|≥128	8	128	73.1	15.4	11.5	≤0.25	>128
Tigecycline	None available	32	>32	-	-	-	1	>32
Tobramycin	≤4|8|≥16	≤0.25	32	84.6	0	15.4	≤0.12	>32
Colistin	≤2|4|≥8	1	1	96.2	1.9	1.9	0.5	>64

%Sus, %Int, %Res; % of isolates susceptible, intermediate or resistant, respectively. SDD, susceptible dose-dependent. Min; minimum MIC. Max; maximum MIC

Table 5. Summary MIC Data and Susceptibility for Antimicrobial Agents Against 35 *K. pneumoniae*

Antimicrobial	CLSI Breakpoints (S|I|R)	MIC50	MIC90	%Sus	%Int	%Res	Min	Max
RX-P873	None available	0.5	1	-	-	-	0.25	2
Ciprofloxacin	≤0.06|0.12-0.5|≥1	0.06	>4	62.9	8.6	28.6	0.015	>4
Meropenem	≤1|2|≥4	0.03	0.06	94.3	0	5.7	0.015	8
Cefepime	≤2|4-8|≥16 [I=SDD]	0.06	>32	74.3	5.7	20.0	0.03	>32
Ceftazidime	≤4|8|≥16	0.25	>32	74.3	0	25.7	0.06	>32
Piperacillin/tazobactam	≤16|32-64|≥128	4	>128	68.6	5.7	25.7	0.5	>128
Tigecycline	≤2|4|≥8 [FDA]	2	4	57.1	37.1	5.7	1	>8
Tobramycin	≤4|8|≥16	0.5	>16	77.1	0	22.9	≤0.12	>16
Colistin	None available	0.5	1	-	-	-	0.5	2

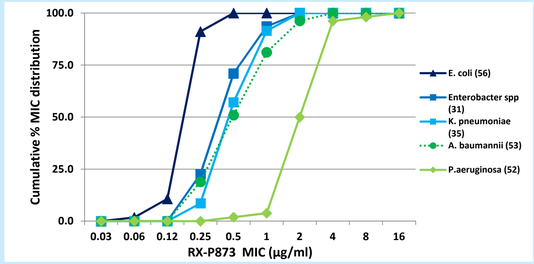
%Sus, %Int, %Res; % of isolates susceptible, intermediate or resistant, respectively. SDD, susceptible dose-dependent. Min; minimum MIC. Max; maximum MIC

Table 6. Summary MIC Data and Susceptibility for Antimicrobial Agents Against 31 *Enterobacter* spp.

Antimicrobial	CLSI Breakpoints (S|I|R)	MIC_{50}	MIC_{90}	%Sus	%Int	%Res	Min	Max
RX-P873	None available	0.5	1	-	-	-	0.25	2
Ciprofloxacin	≤0.06|0.12-0.5|≥1	0.015	1	77.4	6.5	16.1	0.008	2
Meropenem	≤1|2|≥4	0.03	0.12	100	0	0	0.015	0.5
Cefepime	≤2|4-8|≥16 [I=SDD]	0.12	4	83.9	6.5	9.7	0.03	>32
Ceftazidime	≤4|8|≥16	0.5	>32	71.0	0	29.0	0.12	>32
Piperacillin/tazobactam	≤16|32-64|≥128	4	>32	80.6	9.7	9.7	1	>128
Tigecycline	≤2|4|≥8 [FDA]	2	4	83.9	12.9	3.2	0.03	>8
Tobramycin	≤4|8|≥16	0.5	1	93.5	0	6.5	≤0.25	>16
Colistin	None available	0.5	1	-	-	-	0.5	>8

%Sus, %Int, %Res; % of isolates susceptible, intermediate or resistant, respectively. SDD, susceptible dose-dependent. Min; minimum MIC. Max; maximum MIC

Figure 2: Cumulative Percentage MIC distribution for RX-P873.



Conclusions

- RX-P873 showed excellent activity against all the Gram-negative bacterial species tested with narrow MIC distributions.
- RX-P873 was the most active agent tested against *A. baumannii* and *E. coli* with MIC_{90} of 2 and 0.25 µg/ml, respectively and was the joint most active agent (with colistin) against *K. pneumoniae* with MIC_{90} of 2 and 1 µg/ml. Importantly, colistin (MIC_{90} 1 µg/ml) and RX-P873 (MIC_{90} of 4µg/ml) were the most active agents tested against *P. aeruginosa.*
- *Enterobacter* spp. were generally susceptible to test agents, with the exception of ceftazidime and piperacillin/tazobactam. Against these, RX-P873 was active against all isolates with MIC_{90} of 1 µg/ml.
- RX-P873 is therefore a promising new agent for the treatment of problematic Gram-negative bacteria and warrants further investigation

References

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