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Spectrum of Activity of RX-P2382, a Novel Class of Bacterial Ribosome Inhibitor

D Shortridge[1], PR Rhomberg[1], TH Grossman[2], A Bhattacharjee[2], J Ippolito[2], Z Kanyo[2], E Duffy[2], RK Flamm[1]

[1]JMI Laboratories, North Liberty, Iowa, USA; [2]Melinta Therapeutics, New Haven, CT, USA

Contact Information:
Dee Shortridge, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: dee-shortridge@jmilabs.com

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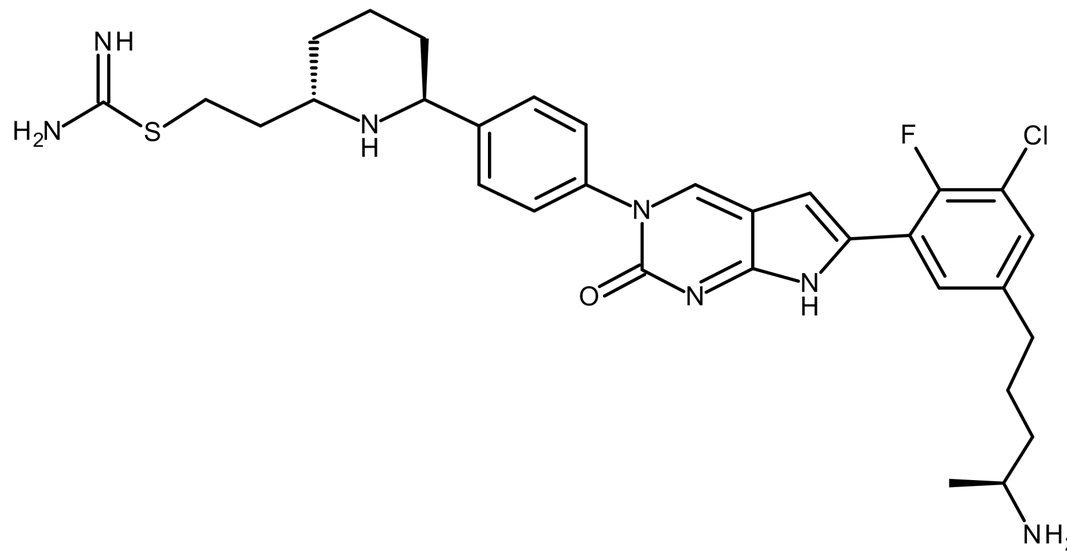
Introduction

- RX-P2382 is an advanced lead of the pyrrolocytosine class, which has been designed *de novo* to target the ribosome with a novel mechanism of inhibition
  - The structure is shown in Figure 1
- This novel class has been optimized to maximize bacterial influx and minimize efflux to show a broad spectrum of *in vitro* activity across the ESKAPE pathogens
- In this study, RX-P2382's spectrum of activity was examined across a broad range of clinical isolates, including recent drug-resistant pathogens from urinary tract, bloodstream, pneumonia, and other infections
  - Isolates were collected during 2016–2017 from hospitals participating in the global SENTRY Antimicrobial Surveillance Program, 45% of which were from urinary tract infections

Figure 1 Structure of RX-P2382



Materials and Methods

- RX-P2382 susceptibilities were determined for 594 Gram-negative (GN) and Gram-positive (GP) clinical isolates
  - Isolates tested included 382 *Enterobacteriaceae* (new taxonomy *Enterobacterales*; ENT), carbapenem-resistant ENT (CRE), 30 *Pseudomonas aeruginosa* (PSA), 31 *Acinetobacter baumannii-calcoaceticus* species complex (ACB), 65 *Enterococcus* spp. including vancomycin-resistant enterococci (VRE), and 32 *Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA)
- JMI Laboratories confirmed all isolate identifications by MALDI-TOF
- Susceptibility testing was performed according to CLSI broth microdilution methodology (M07, M100)
- Isolates were characterized as CRE and extended-spectrum beta-lactamase screen-positive phenotype (ESBL-SP) according to CLSI criteria (M100, 2018)

Results

- RX-P2382 was active against a broad spectrum of clinical isolates, including Gram-negative and Gram-positive pathogens, with a unimodal distribution (Tables 1 and 2)
- The $MIC_{50/90}$ values for RX-P2382 were 0.5/1 mg/L against 382 ENT (Table 1)
  - RX-P2382 $MIC_{50/90}$ values were 0.5/4 mg/L, with a range of 0.25 to 8 mg/L for CRE (n = 28)
  - For ESBL-SP isolates, RX-P2382 $MIC_{50/90}$ values were 0.5/1 mg/L, with a range of 0.25 to 8 mg/L (n = 109)
- The ACB RX-P2382 $MIC_{50/90}$ values were 1/1 mg/L, with a range of 0.25 to 2 mg/L (n = 31; Table 1)
- PSA RX-P2382 $MIC_{50/90}$ values were 2/4 mg/L, with a range of 1 to 4 mg/L (n = 30; Table 1)
  - 6 PSA isolates were carbapenem resistant and showed RX-P2382 MIC values of 2 to 4 mg/L
- RX-P2382 generally had higher MIC values against *Stenotrophomonas maltophilia* ($MIC_{50/90}$ 8/>32 mg/L, with a range of 2 to >32 mg/L; n = 32)
- RX-P2382 was also active against Gram-positive pathogens as shown in Table 2
  - For *Staphylococcus aureus* the $MIC_{50/90}$ were 0.12/0.25 mg/L with a range of 0.06 to 1 mg/L (n = 32) including MRSA ($MIC_{50/90}$ 0.12/0.5; n = 16; Table 2)
  - Against VR *E. faecalis*, RX-P2382 $MIC_{50/90}$ values were 0.12/0.12 mg/L, with a range of 0.06 to 0.12 mg/L (n = 10) and VR *E. faecium* $MIC_{50/90}$ values were 0.25/0.5 mg/L, with a range of 0.06 to 1 mg/L(n = 16; Table 2)
  - RX-P2382 had $MIC_{50/90}$ values of 0.06/0.12 mg/L (n = 22; Table 2) against *Streptococcus pneumoniae*

Conclusions

- RX-P2382, a member of the novel pyrrolocytosine class, showed broad-spectrum *in vitro* activity against a wide range of clinical isolates, including Gram-negative and Gram-positive bacteria from various infection types
- RX-P2382 was also active against antibiotic-resistant isolates regardless of resistance mechanism, including ESBL-phenotype, carbapenem-resistance (CRE), vancomycin-restance (VRE) and methicillin-resistance (MRSA)
- The MIC ranges for RX-P2382 were generally narrow and unimodal
- These data suggest that further evaluation of this novel agent is warranted

Acknowledgements

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References

Clinical and Laboratory Standards Institute (2018). *M100Ed28E. Performance standards for antimicrobial susceptibility testing: 28th informational supplement.* Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute (2018). *M07Ed11E. Methods for dilution antimicrobial susceptibilty tests for bacteria that grow aerobically; approved standard—eleventh edition*. Wayne, PA: CLSI.

Table 1 Antimicrobial activity of RX-P2382 tested against the main organisms and organism groups for Gram-negative species

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of[a]:															MIC_{50}	MIC_{90}
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> [b]		
Enterobacteriaceae																	
RX-P2382 (382)					0 0.0	30 7.9	125 40.6	154 80.9	60 96.6	6 98.2	5 99.5	2 100.0				0.5	1
ESBL-phenotype *Enterobacteriaceae*																	
RX-P2382 (109)						0 0.0	39 35.8	50 81.7	13 93.6	1 94.5	4 98.2	2 100.0				0.5	1
Carbapenem-resistant *Enterobacteriaceae*																	
RX-P2382 (28)						0 0.0	8 28.6	11 67.9	3 78.6	0 78.6	4 92.9	2 100.0				0.5	4
Acinetobacter baumannii-calcoaceticus species complex																	
RX-P2382 (31)						0 0.0	5 16.1	9 45.2	15 93.5	2 100.0						1	1
Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* species complex																	
RX-P2382 (13)							0 0.0	4 30.8	8 92.3	1 100.0						1	1
Pseudomonas aeruginosa																	
RX-P2382 (30)								0 0.0	2 6.7	17 63.3	11 100.0					2	4
Carbapenem-resistant *Pseudomonas aeruginosa*																	
RX-P2382 (5)									0 0.0	2 40.0	3 100.0					4	

[a] Intensity of shading is proportional to the number of tested isolates within each row that displays the indicated MIC value.
[b] Greater than the highest concentration tested.

Table 2 Antimicrobial activity of RX-P2392 tested against the main organisms and organism groups for Gram-positive species

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of[a]:												MIC_{50}	MIC_{90}
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	> [b]		
Enterococcus faecalis															
RX-P2382 (33)			0 0.0	13 39.4	18 93.9	2 100.0								0.12	0.12
Vancomycin-nonsusceptible (VRE) *Enterococcus faecalis*															
RX-P2382 (10)			0 0.0	2 20.0	8 100.0									0.12	0.12
Enterococcus faecium															
RX-P2382 (32)			0 0.0	3 9.4	10 40.6	15 87.5	3 96.9	1 100.0						0.25	0.5
Vancomycin-nonsusceptible (VRE) *Enterococcus faecium*															
RX-P2382 (16)			0 0.0	2 12.5	4 37.5	7 81.2	2 93.8	1 100.0						0.25	0.5
Staphylococcus aureus															
RX-P2382 (32)			0 0.0	8 25.0	17 78.1	5 93.8	1 96.9	1 100.0						0.12	0.25
Methicillin-resistant *S. aureus*															
RX-P2382 (16)			0 0.0	3 18.8	7 62.5	4 87.5	1 93.8	1 100.0						0.12	0.5
Streptococcus pneumoniae															
RX-P2382 (22)			0 0.0	19 86.4	3 100.0									0.06	0.12
Penicillin-nonsusceptible *Streptococcus pneumoniae*															
RX-P2382 (11)			0 0.0	8 72.7	3 100.0									0.06	0.12

[a] Intensity of shading is proportional to the number of tested isolates within each row that displays the indicated MIC value.
[b] Greater than the highest concentration tested.