In Vitro Activity of RX-P873 Tested against Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter* spp.

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ABSTRACT

Background: RX-P873 (RX) is a novel antibiotic which is the lead compound of a series that target a biologically conserved region in the bacterial ribosome. RX is from the pyrrolocytosine series, one of three unique molecular scaffolds with high binding affinity and broad spectrum antibiotic properties. The pyrrolocytosines have shown in vitro activity and preclinical efficacy against multidrug resistant (MDR) Gram-negative and Gram-positive strains of bacteria known to cause complicated urinary tract, skin, and lung infections, as well as sepsis.

Methods: Enterobacteriaceae (657), *P. aeruginosa* (PSA, 200) and *Acinetobacter* spp. (202) isolates from North America and Europe collected in 2012 as part of a worldwide surveillance program were tested in vitro by broth microdilution using Clinical and Laboratory Standards Institute (CLSI) methodology as described in CLSI document M07-A9 (2012). Quality Control (QC) strains were tested daily and QC ranges and interpretive criteria for the comparator compounds were as published in CLSI M100-S24 (2014); tested QC strains were *Escherichia coli* ATCC 25922 and 35218; and PSA ATCC 27853.

Results: RX ($MIC_{50/90}$, 0.25/0.5 µg/ml) was >32 fold more active than ceftazidime (CAZ; MIC_{90}, >16 µg/ml; 82.3% S) and inhibited 97.1 and 99.5% of Enterobacteriaceae isolates at MIC of ≤1 and ≤4 µg/ml, respectively. There were only three isolates with MIC values >4 µg/ml (each were indole-positive Proteae). RX ($MIC_{50/90}$, 2/4 µg/ml) was highly active against PSA including strains non-S to CAZ or meropenem (MER). RX was two-fold less active than tobramycin (MIC_{90}, 2 µg/ml; 91.0% S) and colistin (MIC_{90}, 2 µg/ml; 99.5% S) and two-fold more potent than amikacin (MIC_{90}, 8 µg/ml; 93.5% S) and MER (MIC_{90}, 8 µg/ml; 76.0% S) against PSA. RX, the most active agent against *Acinetobacter* spp. ($MIC_{50/90}$, 0.5/1 µg/ml) was two-fold more active than colistin (MIC_{90}, 2 µg/ml; 97.0% S) and four-fold more active than tigecycline (MIC_{90}, 4 µg/ml). Susceptibility to ciprofloxacin, MER, tobramycin and amikacin ranged from 36.1-58.4%.

Conclusions: RX, a novel agent targeting protein synthesis, exhibited potent activity against Enterobacteriaceae, PSA and *Acinetobacter* spp. This novel agent merits further exploration of its potential against MDR Gram-negative bacteria.

INTRODUCTION

Multidrug-resistant Gram-negative bacilli represent a serious public health problem. The CDC report "Antibiotic Resistance Threats in the United States, 2013" estimates that there are over two million infections annually occurring with antibiotic resistant bacteria and at least 23,000 deaths. A number of Gram-negative bacteria in the report are identified as threats. Among the Gram-negatives included in the threats list are carbapenem-resistant Enterobacteriaceae (CRE), which are listed as an urgent threat. Included among the serious threats are multidrug resistant *Acinetobacter*, multidrug resistant *Pseudomonas aeruginosa,* and extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs).

RX-P873 is a novel antibiotic which represents a series of compounds that target a biologically-conserved region in the bacterial ribosome. RX-P873 is from the pyrrolocytosine series, one of three de novo-designed molecular scaffolds with high binding affinity and properties that have been rationally optimized for broad-spectrum activity. The pyrrolocytosines have shown in vitro activity and preclinical efficacy against multidrug resistant (MDR) Gram-negative and Gram-positive strains of bacteria known to cause complicated urinary tract, skin, and lung infections, as well as sepsis. In this study, we evaluated the spectrum and activity of RX-P873 when tested against contemporary Enterobacteriaceae and non-fermentative Gram-negative bacilli collected in 2012 as part of a worldwide surveillance program.

MATERIALS AND METHODS

Organism Collection: A total of 657 Enterobacteriaceae and 402 non-fermentative Gram-negative bacilli (NF-GNB) isolates collected during 2012 as part of a global surveillance program were selected. Isolates from various medical institutions located in North America and Europe were chosen to represent the contemporary frequency distributions of antimicrobial susceptibility profiles within each organism species or genus group, as follows: *Escherichia coli* (202 strains); *Klebsiella pneumoniae* (202 strains); *Enterobacter cloacae* (50 strains); *Enterobacter aerogenes* (50 strains); *Citrobacter freundii* (51 strains); *Proteus* spp. (51 strains); *Serratia marcescens* (51 strains); *P. aeruginosa* (200 strains); *Acinetobacter baumannii* (202 strains).

Susceptibility testing: MIC values were determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology as described in CLSI document M07-A9 (2012). The compound RX-P873 (**Figure 1**) and comparator agents were tested in 96-well, frozen-form panels produced by JMI Laboratories (North Liberty, Iowa, USA) and consisted of one reference media type, cation-adjusted Mueller-Hinton broth. Two individual lots of 96-well panels were produced to accommodate testing the appropriate comparator agents against the two distinct non-fermentative pathogen groups. Quality Control (QC) strains were tested daily and inoculum density was monitored by colony counts. QC ranges and interpretive criteria for the comparator compounds were as published in CLSI M100-S23 (2013); tested QC strains were *E. coli* ATCC 25922 and 35218 and *P. aeruginosa* ATCC 27853.

RESULTS

Enterobacteriaceae

- The range of RX-P873 MIC values was 0.06 to ≥32 µg/ml with MIC_{50} and MIC_{90} values of 0.25 and 0.5 µg/ml, respectively (**Table 1**). Only four of the 657 isolates (0.6%) had reproducible MIC values >2 µg/ml for RX-P873; one strain (*Proteus mirabilis*) with a MIC of 4 µg/ml, one strain (*Providencia stuartii*) with a MIC of 8 µg/ml, one strain (*Providencia rettgeri*) with a MIC of 16 µg/ml, and one strain (*P. stuartii*) with a MIC of >32 µg/ml. Against the majority of isolates, RX-P873 was the second most potent agent tested (MIC_{90}, 0.5 µg/ml) with meropenem being the most potent (MIC_{90}, ≤0.06 µg/ml; **Table 2**).
- Against *E. coli* the range of RX-P873 MIC values was 0.06 to 2 µg/ml with MIC_{50} and MIC_{90} values of 0.12 and 0.25 µg/ml, respectively (**Table 1** and **2**). RX-P873 had identical potency to tigecycline (MIC_{50} and MIC_{90}, 0.12 and 0.25 µg/ml for both agents) with meropenem being the most potent (MIC_{90}, ≤0.06 µg/ml; **Table 2**).
- Against *K. pneumoniae*, the range of RX-P873 MIC values was 0.12 to 2 µg/ml with MIC_{50} and MIC_{90} values of 0.25 and 0.5 µg/ml, respectively (**Table 1**). Meropenem resistance was 5.0%/4.5% by CLSI/EUCAST criteria, respectively, and resistance to all other comparator agents (except tigecycline) ranged from 2.5% for colistin (EUCAST criteria) to 23.3% for ceftazidime (EUCAST criteria; **Table 2**). RX-P873 inhibited all isolates at MIC values ≤2 µg/ml, similar to tigecycline (all isolates inhibited at MIC ≤4 µg/ml).
- Against *E. cloacae,* the range of RX-P873 MIC values was 0.12 to 1 µg/ml with MIC_{50} and MIC_{90} values of 0.5 and 0.5 µg/ml, respectively (**Table 2**). All isolates were inhibited by meropenem at MIC values ≤2 µg/ml (98.0%/100.0% susceptible by CLSI/EUCAST interpretive criteria). Resistance rates (CLSI) for other agents ranged from 2.0% for tigecycline to 46.0% for ceftriaxone. For colistin, 12.0% of isolates were found to be resistant by EUCAST interpretive criteria (**Table 2**). RX-P873 retained activity against all of these resistance phenotypes, inhibiting all 50 strains at MIC values ≤1 µg/ml.
- The range of RX-P873 MIC values against 50 *E. aerogenes* was 0.12 to 1 µg/ml with MIC_{50} and MIC_{90} values of 0.25 and 0.5 µg/ml, respectively (**Table 1**). All isolates were inhibited by meropenem at MIC values ≤0.25 µg/ml (100.0% susceptible by CLSI and EUCAST interpretive criteria). Resistance rates (CLSI) for other agents ranged from 0.0% for tigecycline to 46.0% for ceftriaxone. For colistin, 4.0% of isolates were found to be resistant by EUCAST interpretive criteria (**Table 2**). RX-P873 retained activity against all resistance phenotypes, inhibiting all 50 strains at MIC values ≤1 µg/ml.
- The range of RX-P873 MIC values against 51 *C. freundii* was 0.12 to 2 µg/ml with MIC_{50} and MIC_{90} values of 0.25 and 0.5 µg/ml, respectively (**Table 1**). Meropenem resistance was 3.9% by CLSI and EUCAST criteria and resistance (CLSI criteria) to all other comparator agents (except tigecycline) ranged from 5.9% for gentamicin and cefepime to 23.5% for ceftriaxone (**Table 2**). RX-P873 and tigecycline inhibited all isolates at MIC values ≤2 µg/ml (USA-FDA susceptible breakpoint). All isolates were susceptible to colistin (EUCAST criteria).
- Other than the four strains mentioned above, RX-P873 inhibited the remaining 47 isolates of *Proteus* spp. at MIC values ≤2 µg/ml, with MIC_{50} and MIC_{90} values of 1 and 2 µg/ml, respectively, which represent the highest MIC parameters observed for all seven species/groups tested (**Table 1**).
- The range of RX-P873 MIC values against 51 *S. marcescens* was 0.12 to 2 µg/ml with MIC_{50} and MIC_{90} values of 0.5 and 0.5 µg/ml, respectively (**Table 1**).
- Against all 402 strains of NF-GNB tested, the range of RX-P873 MIC values was 0.12 to 8 µg/ml with MIC_{50} and MIC_{90} values of 1 and 4 µg/ml, respectively (**Table 1**).

Non-fermentative Gram-negative bacilli

- The range of RX-P873 MIC values against 200 *P. aeruginosa* was 0.25 to 8 µg/ml with MIC_{50} and MIC_{90}values of 2 and 4 µg/ml, respectively (**Table 1**). For β-lactam agents, non-susceptibility ranged from 15.5% for cefepime to 24.0% for meropenem. For non-β-lactam agents, non-susceptibility ranged from 0.5% for colistin to 22.0% (CLSI) for ciprofloxacin (**Table 2**). RX-P873 and colistin were the most potent agents tested.
- Against *A. baumannii* the range of RX-P873 MIC values was 0.12 to 4 µg/ml with MIC_{50} and MIC_{90}values of 0.5 and 1 µg/ml, respectively (**Table 1**). For β-lactam agents, non-susceptibility ranged from 52.0% for ampicillin/sulbactam to 63.4% for cefepime. Meropenem resistance was 52.5%. For non-β-lactam agents, non-susceptibility ranged from 3.0% for colistin to 63.9% for ciprofloxacin (**Table 2**). RX-P873 was the most potent agent tested.

Table 1. Cumulative MIC distribution for RX-P873 when tested against 657 Enterobacteriaceae and 402 non-fermentative Gram-negative bacilli.

Organism group (no. tested)	No. of strains at MIC (µg/ml; cumulative %):											MIC (µg/ml)	
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥32	50%	90%
Enterobacteriaceae (657)	0 (0.0)	0 (0.0)	2 (0.3)	188 (28.9)	287 (72.6)	122 (91.2)	39 (97.1)	15 (99.4)	1 (99.5)	1 (99.7)	1 (99.8)	1 (100.0)	0.25	0.5
E. coli (202)	0 (0.0)	0 (0.0)	2 (1.0)	111 (55.9)	78 (94.6)	8 (98.5)	2 (99.5)	1 (100.0)					0.12	0.25
K. pneumoniae (202)	0 (0.0)	0 (0.0)	0 (0.0)	52 (25.7)	117 (83.7)	28 (97.5)	2 (98.5)	3 (100.0)					0.25	0.5
E. cloacae (50)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.0)	21 (48.0)	23 (94.0)	3 (100.0)						0.5	0.5
E. aerogenes (50)	0 (0.0)	0 (0.0)	0 (0.0)	14 (28.0)	30 (88.0)	5 (98.0)	1 (100.0)						0.25	0.5
C. freundii (51)	0 (0.0)	0 (0.0)	0 (0.0)	5 (9.8)	22 (52.9)	19 (90.2)	4 (98.0)	1 (100.0)					0.25	0.5
Proteus spp. (51)[a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	4 (9.8)	9 (27.5)	24 (74.5)	9 (92.2)	1 (94.1)	1 (96.1)	1 (98.0)	1 (100.0)	1	2
S. marcescens (51)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	15 (33.3)	30 (92.2)	3 (98.0)	1 (100.0)					0.5	0.5
Non-fermentative bacilli (402)	0 (0.0)	0 (0.0)	0 (0.0)	9 (2.2)	41 (12.4)	85 (33.6)	136 (67.4)	77 (86.6)	45 (97.8)	9 (100.0)			1	4
P. aeruginosa (200)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	5 (3.0)	76 (41.0)	70 (76.0)	39 (95.5)	9 (100.0)			2	4
A. baumannii (202)	0 (0.0)	0 (0.0)	0 (0.0)	9 (4.5)	40 (24.3)	80 (63.9)	60 (93.6)	7 (97.0)	6 (100.0)				0.5	1

a. Includes the following species (n): *Proteus mirabilis* (30), *Morganella morganii* (11), *Proteus. vulgaris* (four), *Providencia rettgeri* (four), and *Providencia stuartii* (two).

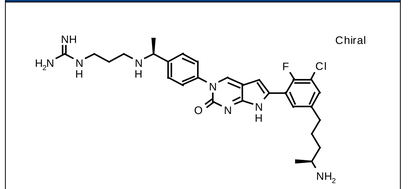
Table 2. Activity of RX-P873 and comparator antimicrobial agents when tested against 657 Enterobacteriaceae and 402 non-fermentative Gram-negative bacilli.

Organism group (no. tested)/ antimicrobial agent	MIC (µg/ml)			% Susceptible/ % Intermediate/ % Resistant	
	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
Enterobacteriaceae (657)[b]					
RX-P873	0.25	0.5	0.06 – >32	- / - / -	- / - / -
Pip/taz[c]	2	32	≤0.5 – >64	87.5 / 6.3 / 6.2	83.9 / 3.6 / 12.5
Ceftriaxone	0.06	>2	≤0.015 – >2	79.6 / 0.3 / 20.1	79.6 / 0.3 / 20.1
Ceftazidime	0.25	>16	≤0.12 – >16	82.3 / 1.9 / 15.8	79.3 / 3.0 / 17.7
Cefepime	≤0.12	8	≤0.12 – >16	91.0 / 2.9 / 6.1	85.5 / 4.1 / 10.4
Ciprofloxacin	0.03	>8	≤0.004 – >8	83.1 / 2.0 / 14.9	81.6 / 1.5 / 16.9
Colistin	0.5	>8	≤0.12 – >8	- / - / -	83.3 / 0.0 / 16.7
Gentamicin	0.5	2	≤0.06 – >8	92.4 / 0.3 / 7.3	91.0 / 1.4 / 7.6
Meropenem	≤0.06	≤0.06	≤0.06 – >8	98.0 / 0.2 / 1.8	98.2 / 0.1 / 1.7
Tigecycline[d]	0.5	2	0.06 – >4	97.1 / 2.6 / 0.3	88.9 / 8.2 / 2.9
E. coli (202)					
RX-P873	0.12	0.25	0.06 – 2	- / - / -	- / - / -
Pip/taz	2	8	≤0.5 – >64	93.1 / 3.4 / 3.5	90.6 / 2.5 / 6.9
Ceftriaxone	0.06	>2	≤0.015 – >2	88.6 / 0.0 / 11.4	88.6 / 0.0 / 11.4
Ceftazidime	0.25	2	≤0.12 – >16	93.1 / 1.0 / 5.9	89.1 / 4.0 / 6.9
Cefepime	≤0.12	2	≤0.12 – >16	92.6 / 2.9 / 4.5	89.1 / 3.0 / 7.9
Ciprofloxacin	0.015	>8	0.008 – >8	78.2 / 1.0 / 20.8	77.7 / 0.5 / 21.8
Colistin	0.25	0.5	0.25 – 0.5	- / - / -	100.0 / 0.0 / 0.0
Gentamicin	0.5	1	≤0.06 – >8	93.1 / 0.5 / 6.4	92.1 / 1.0 / 6.9
Meropenem	≤0.06	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Tigecycline[d]	0.12	0.25	0.06 – 1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
K. pneumoniae (202)					
RX-P873	0.25	0.5	0.12 – 2	- / - / -	- / - / -
Pip/taz	2	32	≤0.5 – >64	88.1 / 3.0 / 8.9	83.7 / 4.4 / 11.9
Ceftriaxone	0.06	>2	≤0.015 – >2	77.7 / 0.0 / 22.3	77.7 / 0.0 / 22.3
Ceftazidime	0.25	>16	≤0.12 – >16	76.7 / 3.5 / 19.8	75.2 / 1.5 / 23.3
Cefepime	≤0.12	>16	≤0.12 – >16	83.2 / 4.9 / 11.9	78.7 / 2.5 / 18.8
Ciprofloxacin	0.03	>8	0.008 – >8	80.2 / 2.5 / 17.3	79.7 / 0.5 / 19.8
Colistin	0.5	1	0.25 – >8	- / - / -	97.5 / 0.0 / 2.5
Gentamicin	0.25	>8	≤0.06 – >8	89.1 / 0.0 / 10.9	87.6 / 1.5 / 10.9
Meropenem	≤0.06	≤0.06	≤0.06 – >8	95.1 / 0.1 / 5.0	95.1 / 0.4 / 4.5
Tigecycline[d]	0.5	2	0.12 – 4	96.5 / 3.5 / 0.0	88.6 / 7.9 / 3.5
E. cloacae (50)					
RX-P873	0.5	0.5	0.12 – 1	- / - / -	- / - / -
Pip/taz	4	>64	1 – >64	70.0 / 12.0 / 18.0	64.0 / 6.0 / 30.0
Ceftriaxone	1	>2	0.03 – >2	54.0 / 0.0 / 46.0	54.0 / 0.0 / 46.0
Ceftazidime	0.5	>16	≤0.12 – >16	60.0 / 2.0 / 38.0	54.0 / 6.0 / 40.0
Cefepime	≤0.12	8	≤0.12 – >16	92.0 / 2.0 / 6.0	72.0 / 14.0 / 14.0
Ciprofloxacin	0.015	8	0.008 – >8	80.0 / 6.0 / 14.0	80.0 / 0.0 / 20.0
Colistin	0.5	8	0.25 – >8	- / - / -	88.0 / 0.0 / 12.0
Gentamicin	0.25	>8	0.12 – >8	88.0 / 0.0 / 12.0	84.0 / 4.0 / 12.0
Meropenem	≤0.06	0.12	≤0.06 – 2	98.0 / 2.0 / 0.0	100.0 / 0.0 / 0.0
Tigecycline[d]	0.5	2	0.25 – >4	90.0 / 8.0 / 2.0	84.0 / 6.0 / 10.0
E. aerogenes (50)					
RX-P873	0.25	0.5	0.12 – 1	- / - / -	- / - / -
Pip/taz	4	64	≤0.5 – >64	64.0 / 32.0 / 4.0	56.0 / 8.0 / 36.0
Ceftriaxone	0.25	>2	≤0.015 – >2	54.0 / 0.0 / 46.0	54.0 / 0.0 / 46.0
Ceftazidime	1	>16	≤0.12 – >16	54.0 / 2.0 / 44.0	52.0 / 2.0 / 46.0
Cefepime	≤0.12	2	≤0.12 – 16	98.0 / 2.0 / 0.0	88.0 / 10.0 / 2.0
Ciprofloxacin	0.015	0.5	0.008 – >8	94.0 / 0.0 / 6.0	90.0 / 4.0 / 6.0
Colistin	0.25	0.5	0.25 – >8	- / - / -	96.0 / 0.0 / 4.0
Gentamicin	0.25	1	0.12 – >8	96.0 / 0.0 / 4.0	92.0 / 6.0 / 2.0
Meropenem	≤0.06	0.12	≤0.06 – 0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Tigecycline[d]	0.5	1	0.12 – 4	98.0 / 2.0 / 0.0	92.0 / 6.0 / 2.0

Organism group (no. tested)/ antimicrobial agent	MIC (µg/ml)			% Susceptible/ % Intermediate/ % Resistant	
	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
C. freundii (51)					
RX-P873	0.25	0.5	0.12 – 2	- / - / -	- / - / -
Pip/taz	2	64	≤0.5 – >64	82.4 / 7.8 / 9.8	78.4 / 4.0 / 17.6
Ceftriaxone	0.25	>2	0.06 – >2	76.5 / 0.0 / 23.5	76.5 / 0.0 / 23.5
Ceftazidime	0.5	>16	0.25 – >16	78.4 / 0.0 / 21.6	72.5 / 5.9 / 21.6
Cefepime	≤0.12	4	≤0.12 – >16	92.2 / 1.9 / 5.9	86.3 / 5.9 / 7.8
Ciprofloxacin	0.06	2	0.008 – >8	86.3 / 3.9 / 9.8	80.4 / 5.9 / 13.7
Colistin	0.5	1	≤0.12 – 1	- / - / -	100.0 / 0.0 / 0.0
Gentamicin	0.5	1	0.12 – >8	92.2 / 1.9 / 5.9	90.2 / 2.0 / 7.8
Meropenem	≤0.06	≤0.06	≤0.06 – >8	96.1 / 0.0 / 3.9	96.1 / 0.0 / 3.9
Tigecycline[d]	0.25	1	0.12 – 2	100.0 / 0.0 / 0.0	92.2 / 7.8 / 0.0
Proteus spp. (51)[a]					
RX-P873	1	2	0.12 – >32	- / - / -	- / - / -
Pip/taz	≤0.5	≤0.5	≤0.5 – 4	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Ceftriaxone	≤0.015	0.06	≤0.015 – >2	96.1 / 0.0 / 3.9	96.1 / 0.0 / 3.9
Ceftazidime	≤0.12	≤0.12	≤0.12 – 8	98.0 / 2.0 / 0.0	96.1 / 1.9 / 2.0
Cefepime	≤0.12	≤0.12	≤0.12 – 8	100.0 / 0.0 / 0.0	96.1 / 1.9 / 2.0
Ciprofloxacin	0.03	2	≤0.004 – >8	88.2 / 2.0 / 9.8	86.3 / 1.9 / 11.8
Colistin	>8	>8	>8	- / - / -	0.0 / 0.0 / 100.0
Gentamicin	0.5	2	0.12 – >8	98.0 / 0.0 / 2.0	96.1 / 1.9 / 2.0
Meropenem	≤0.06	0.12	≤0.06 – 0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Tigecycline[d]	1	2	0.12 – >4	92.2 / 5.8 / 2.0	52.9 / 39.3 / 7.8
S. marcescens (51)					
RX-P873	0.5	0.5	0.12 – 2	- / - / -	- / - / -
Pip/taz	2	8	≤0.5 – 64	96.1 / 3.9 / 0.0	94.1 / 2.0 / 3.9
Ceftriaxone	0.25	2	0.03 – >2	88.2 / 4.8 / 7.8	88.2 / 4.0 / 7.8
Ceftazidime	0.25	0.5	≤0.12 – 4	100.0 / 0.0 / 0.0	98.0 / 2.0 / 0.0
Cefepime	≤0.12	0.25	≤0.12 – >16	98.0 / 0.0 / 2.0	98.0 / 0.0 / 2.0
Ciprofloxacin	0.06	0.12	0.015 – >8	98.0 / 0.0 / 2.0	94.1 / 3.9 / 2.0
Colistin	>8	>8	1 – >8	- / - / -	9.8 / 0.0 / 90.2
Gentamicin	0.5	1	0.12 – >8	98.0 / 0.0 / 2.0	98.0 / 0.0 / 2.0
Meropenem	≤0.06	0.12	≤0.06 – 0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Tigecycline[d]	1	2	0.5 – 4	96.1 / 3.9 / 0.0	80.4 / 15.7 / 3.9
P. aeruginosa (200)					
RX-P873	2	4	0.25 – 8	- / - / -	- / - / -
Pip/taz	4	64	≤0.5 – >64	80.5 / 11.0 / 8.5	80.5 / 0.0 / 19.5
Ceftazidime	2	>16	0.5 – >16	83.0 / 4.0 / 13.0	83.0 / 0.0 / 17.0
Cefepime	2	16	0.25 – >16	84.5 / 10.5 / 5.0	84.5 / 0.0 / 15.5
Ciprofloxacin	0.12	>8	0.008 – >8	78.0 / 2.0 / 20.0	76.0 / 2.0 / 22.0
Tobramycin	0.5	2	≤0.25 – >16	91.0 / 1.5 / 7.5	91.0 / 0.0 / 9.0
Amikacin	4	8	≤0.25 – >32	93.5 / 2.0 / 4.5	91.0 / 2.5 / 6.5
Meropenem	0.5	8	≤0.06 – >8	76.0 / 6.0 / 18.0	76.0 / 14.5 / 9.5
Colistin	1	2	0.25 – 4	99.5 / 0.5 / 0.0	100.0 / 0.0 / 0.0
A. baumannii (202)					
RX-P873	0.5	1	0.12 – 4	- / - / -	- / - / -
Ampicillin/sulbactam	16	>32	0.5 – >32	48.0 / 11.4 / 40.6	- / - / -
Ceftazidime	>16	>16	0.5 – >16	38.1 / 2.5 / 59.4	- / - / -
Cefepime	16	>16	0.25 – >16	36.6 / 13.4 / 50.0	- / - / -
Ciprofloxacin	>8	>8	0.06 – >8	36.1 / 0.0 / 63.9	36.1 / 0.0 / 63.9
Tobramycin	4	>16	≤0.25 – >16	53.5 / 3.4 / 43.1	53.5 / 0.0 / 46.5
Amikacin	8	>32	≤0.25 – >32	58.4 / 6.0 / 35.6	53.5 / 4.9 / 41.6
Meropenem	>8	>8	≤0.06 – >8	46.0 / 1.5 / 52.5	45.5 / 2.0 / 52.5
Colistin	1	2	0.25 – >8	97.0 / 0.0 / 3.0	97.0 / 0.0 / 3.0
Tigecycline	1	4	0.12 – >4	- / - / -	- / - / -

a. Criteria as published by the CLSI [2013] and EUCAST [2013].
b. Includes: *Citrobacter freundii* (51 strains), *Enterobacter aerogenes* (50 strains), *Enterobacter cloacae* (50 strains), *Escherichia coli* (202 strains), *Klebsiella pneumoniae* (202 strains), *Morganella morganii* (11 strains), *Proteus mirabilis* (30 strains), *Proteus vulgaris* (four strains), *Providencia rettgeri* (four strains), *Providencia stuartii* (two strains), and *Serratia marcescens* (51 strains).
c. Piperacillin/tazobactam.
d. In the absence of CLSI breakpoint, USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2013].
e. Includes: *Morganella morganii* (11 strains), *Proteus mirabilis* (30 strains), *Proteus vulgaris* (four strains), *Providencia rettgeri* (four strains), and *Providencia stuartii* (two strains).

Figure 1. Chemical structure of RX-P873.



CONCLUSIONS

- RX-P873 demonstrated high and consistent potency against this contemporary (2012) set of Enterobacteriaceae and non-fermentative bacilli selected from various medical institutions located in North America and Europe to represent the contemporary frequency distributions of antimicrobial susceptibility profiles for uncomplicated and complicated urinary tract infections and complicated intra-abdominal infections.
- RX-P873 was shown to be very active against Enterobacteriaceae strains with acquired and intrinsic resistance to piperacillin/tazobactam, ceftriaxone, ceftazidime, cefepime, ciprofloxacin, colistin, gentamicin, meropenem and tigecycline.
- RX-P873 was shown to be very active against isolates of *P. aeruginosa* and *A. baumannii* with acquired and intrinsic resistance to piperacillin/tazobactam, ampicillin/sulbactam, ceftazidime, cefepime, meropenem, ciprofloxacin, colistin, tobramycin, amikacin and tigecycline.

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