In Vitro Activity of KHP-3757 and Comparators against Recent and Molecularly Characterized Pseudomonas aeruginosa Isolates from a Global Surveillance Program

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Introduction

- KHP-3757 is a novel LpxC inhibitor with potent in vitro activity against gram-negative bacterial species, including Pseudomonas aeruginosa (Table 1)
- The antibacterial activity of KHP-3757 was examined against 116 P. aeruginosa isolates that included 10 colistin-resistant (R), 6 extended-spectrum β-lactamase (ESBL)-producing, and 7 metallo-β-lactamase (MBL)-producing strains
- KHP-3757 is currently in preclinical development

Materials and Methods

- KHP-3757 activity was evaluated against P. aeruginosa isolates collected in 2017–2018 from patients in 20 countries that included the United States (n=52), Europe (n=63), and the Asia Pacific (n=1) region
- Isolates were collected from patients with bloodstream infection (46 isolates; 39.7%), skin and skin structure infection (34 isolates; 29.3%), and pneumonia (36 isolates; 31.0%) and included 1 isolate/patient/infection episode
- Bacterial identifications were confirmed by JMI Laboratories using matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)
- Broth microdilution susceptibility testing was performed according to Clinical and Laboratory Standards Institute Guidelines (CLSI; M07, 2018), and results were interpreted using CLSI M100 (2019) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2019; v 9.0) breakpoint interpretive criteria

Acknowledgements

References

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Results

- KHP-3757 (MIC$_{50/90}$, 0.25/0.5 mg/L; 97.4% inhibited at ≤0.5 mg/L) was the most active compound tested against a collection of 116 recent and molecularly characterized P. aeruginosa isolates (Table 1)
- P. aeruginosa susceptibility (S) rates (CLSI/EUCAST) for amikacin, ceftazidime, ciprofloxacin, meropenem, and piperacillin-tazobactam were 81.0%/75.0%S, 69.8%/69.8%S, 63.5%/63.5%S, 67.2%/67.2%S, and 67.2%/67.2%S, respectively (Table 1)
- In addition to KHP-3757, colistin (MIC$_{50/90}$, 0.5/2 mg/L; 91.4%/91.4%S [CLSI/EUCAST]) was the only comparator agent with >90.0%S against P. aeruginosa (Table 1)
- KHP-3757 (MIC$_{50/90}$, 0.12/0.5 mg/L; 100.0% inhibited at ≤0.5 mg/L) was the most active compound tested against a collection of 10 colistin-R P. aeruginosa isolates (Table 2); comparator agent susceptibilities ranged from 0.0% for colistin to 70.0% for meropenem (Table 2)
- KHP-3757 (MIC$_{50/90}$, 0.25/0.5 mg/L; 100.0% inhibited at 0.5 mg/L) and colistin (MIC$_{50/90}$, 1/2 mg/L; 100.0%/100.0%S [CLSI/EUCAST]) were the most active agents tested against a collection of 13 ESBL (PER, PME, SHV, GES, and VEB)- or MBL (IMP, VIM, NDM)-producing P. aeruginosa isolates where S to cefepime, ceftazidime, imipenem, and meropenem was 0.0% (Table 3)

Conclusions

- KHP-3757 (MIC$_{50/90}$, 0.25/0.5 mg/L; 97.4% inhibited at ≤0.5 mg/L) demonstrated potent in vitro activity against recent and molecularly characterized P. aeruginosa isolates, including isolates displaying colistin-R, ESBL-producing, and MBL-producing strains and outperformed all comparator agents
- These in vitro results support the continued development of KHP-3757 for the treatment of serious infections caused by susceptible and drug-resistant P. aeruginosa isolates

Table 1 Activity of KHP-3757 and comparators against 116 recent and molecularly characterized P. aeruginosa isolates collected during 2017–2018

Antimicrobial agent	MIC$_{50}$	MIC$_{90}$	CLSI[a]			EUCAST[a]		
			%S	%I	%R	%S	%I	%R
KHP-3757	0.25	0.5	97.4[b]			97.4[b]		
Ceftazidime	2	>32	69.8	7.8	22.4	69.8		30.2
Colistin	0.5	2	91.4		8.6	91.4		8.6
Meropenem	0.5	>8	67.2	6.0	26.7	67.2	9.5	23.3
Amikacin	4	>32	81.0	4.3	14.7	75.0	6.0	19.0
Aztreonam	8	>16	59.5	15.5	25.0	75.0		25.0
Cefepime	4	>16	71.6	12.9	15.5	71.6		28.4
Ciprofloxacin	0.25	>4	63.5	7.0	29.6	63.5		36.5
Imipenem	1	>8	66.4	2.6	31.0	69.0		31.0
Piperacillin-tazobactam	8	128	67.2	15.6	17.2	67.2		32.8

[a] Criteria as published by CLSI (2019) and EUCAST (2019).
[b] Percentage inhibited at ≤0.5 mg/L for comparison purposes only; highest MIC was 2 mg/L.

Table 2 Activity of KHP-3757 and comparators against 10 colistin-resistant P. aeruginosa isolates

Compound tested	No. and cumulative % of isolates inhibited at MIC (mg/L) of:													>[a]	MIC$_{50}$	MIC$_{90}$
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64			
KHP-3757[b]	1 10.0	1 20.0	0 20.0	3 50.0	3 80.0	2 100.0									0.12	0.5
Amikacin							0 0.0	1 10.0	1 20.0	2 40.0	2 60.0	0 60.0		4 100.0	16	>32
Aztreonam					0 0.0	1 10.0	0 10.0	1 20.0	2 40.0	0 40.0	2 60.0			4 100.0	16	>16
Cefepime					0 0.0	1 10.0	0 10.0	2 30.0	3 60.0	2 80.0				2 100.0	8	>16
Ceftazidime				0 0.0	1 10.0	1 20.0	2 40.0	1 50.0	0 50.0	1 60.0	2 80.0			2 100.0	4	>32
Ciprofloxacin				0 0.0	1 10.0	1 20.0	2 40.0	1 50.0	0 50.0					5 100.0	2	>4
Colistin							0 0.0	2 20.0	0 20.0	4 60.0				4 100.0	16	>32
Imipenem					0 0.0	1 10.0	3 40.0	1 50.0	3 80.0	2 100.0					1	8
Meropenem	1 10.0	0 10.0	0 10.0	1 20.0	0 20.0	2 40.0	1 50.0	2 70.0	0 70.0	0 70.0				3 100.0	1	>8
Piperacillin-tazobactam				0 0.0	1 10.0	0 10.0	0 10.0	2 30.0	1 40.0	2 60.0	0 60.0	1 70.0		3 100.0	16	128

[a] MIC value is greater than the highest concentration tested.
[b] KHP-3757 MIC values ≤0.5 highlighted as susceptible for comparison purposes only.
Green, susceptible according to CLSI breakpoint interpretive criteria.
Yellow, intermediate according to CLSI breakpoint interpretive criteria.
Red, resistant according to CLSI breakpoint interpretive criteria.

Table 3 Activity of KHP-3757 and comparators against 13 ESBL- or MBL-producing P. aeruginosa isolates

Compound tested	No. and cumulative % of isolates inhibited at MIC (mg/L) of:													>[a]	MIC$_{50}$	MIC$_{90}$
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64			
KHP-3757[b]			0 0.0	2 15.4	6 61.5	5 100.0									0.25	0.5
Amikacin								0 0.0	2 15.4	0 15.4	2 30.8			9 100.0	>32	>32
Aztreonam							0 0.0	2 15.4	3 38.5	2 53.8				6 100.0	16	>16
Cefepime									0 0.0	4 30.8				9 100.0	>16	>16
Ceftazidime									0 0.0	2 15.4	2 30.8			9 100.0	>32	>32
Ciprofloxacin	0 0.0	1 7.7	1 15.4	1 23.1	0 23.1	0 23.1	0 23.1	1 30.8						9 100.0	>4	>4
Colistin			0 0.0	5 38.5	6 84.6	2 100.0									1	2
Imipenem							0 0.0	3 23.1						10 100.0	>8	>8
Meropenem							0 0.0	1 7.7	2 23.1					10 100.0	>8	>8
Piperacillin-tazobactam								0 0.0	2 15.4	2 30.8	2 46.2			7 100.0	128	>128

ESBL, extended-spectrum β lactamase; MBL, metallo-β-lactamase
[a] MIC value is greater than the highest concentration tested.
[b] KHP-3757 MIC values ≤0.5 highlighted as susceptible for comparison purposes only.
Green, susceptible according to CLSI breakpoint interpretive criteria.
Yellow, intermediate according to CLSI breakpoint interpretive criteria.
Red, resistant according to CLSI breakpoint interpretive criteria.