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Activity of KBP-7072 against Recent and Molecularly Characterized *Acinetobacter baumannii* Isolates

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Introduction

- KBP-7072 is a novel third-generation tetracycline (aminotetracycline; Figure 1) with potent activity against gram-positive, -negative, and anaerobic bacterial isolates (Table 1)
- The antibacterial activity of KBP-7072 and comparators was examined against 531 geographically diverse *Acinetobacter baumannii* isolates, including 38 colistin-resistant (R), 5 extended-spectrum β-lactamase (ESBL)-producing, and 5 metallo-β-lactamase (MBL)-producing strains
- KBP-7072 recently completed phase 1 clinical trials (NCT02454361 and NCT02654626)

Materials and Methods

- KBP-7072 activity was evaluated against 531 *A. baumannii* isolates collected in 2001–2018 (98.1% from 2018) from patients in 34 countries, including the United States (61 medical centers; 169 isolates; 31.8%), Europe (29 medical centers; 171 isolates; 32.2%), Latin America (9 medical centers; 81 isolates; 15.3%), and the Asia Pacific region (17 medical centers; 110 isolates; 20.7%)
- Isolates were collected from patients with bloodstream infections (115 isolates; 21.7%), skin and skin structure infections (113 isolates; 21.3%), pneumonia in hospitalized patients (301 isolates; 56.7%), and urinary tract infections (2 isolates; 0.4%) according to a common surveillance design 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 (CLSI) guidelines (M07, 2018), and results were interpreted using CLSI M100 (2019), European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2019; v 9.0), and FDA breakpoint interpretive criteria

Results

- KBP-7072 ($MIC_{50/90}$, 0.25/1 mg/L; 99.2% inhibited at ≤2 mg/L) was the most active compound tested against a collection of 531 recent and molecularly characterized *A. baumannii* isolates (Table 1)
- Susceptibility (S) of *A. baumannii* isolates to tetracycline-class comparators was 79.5%S, 67.3%S, 73.8%S, and 37.2%S for tigecycline, doxycycline, minocycline, and tetracycline, respectively (Table 1)
- In addition to KBP-7072, colistin ($MIC_{50/90}$, ≤0.5/1 mg/L; 92.8%/92.8%S [CLSI/EUCAST) was the only comparator agent with >90.0%S against *A. baumannii* (Table 1)
- KBP-7072 ($MIC_{50/90}$, 0.5/1 mg/L) was the most active compound tested against a collection of 38 colistin-R *A. baumannii* inhibiting all isolates (100.0%) at ≤2 mg/L (Table 2 and Figure 2); comparator agent susceptibilities ranged from 13.9% for piperacillin-tazobactam to 45.5% for minocycline (Table 2)
- KBP-7072 was the most active agent tested against 5 ESBL- (GES- and CTX-M-) and 5 MBL-producing (IMP- and NDM-) *A. baumannii* isolates with MIC value ranges of 0.06-0.5 mg/L and 0.12-1 mg/L, respectively (Table 3); comparator agents ceftazidime, levofloxacin, and meropenem were inactive against these 10 isolates with MIC values of >16, >4, and >8 mg/L, respectively
- KBP-7072 was 4- to 8-fold more active by MIC than tigecycline against ESBL-producing *A. baumannii* and 2- to 4-fold more active against MBL-producing *A. baumannii* (Table 3)

Figure 1 KBP-7072 compound structure

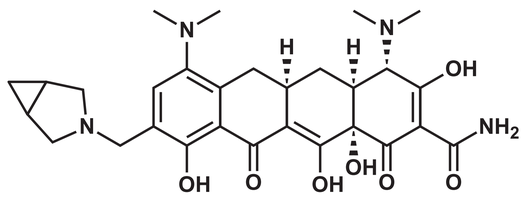

Figure 2 *In vitro* Activity of KBP-7072 and comparators against 38 colistin-resistant *A. baumannii* isolates

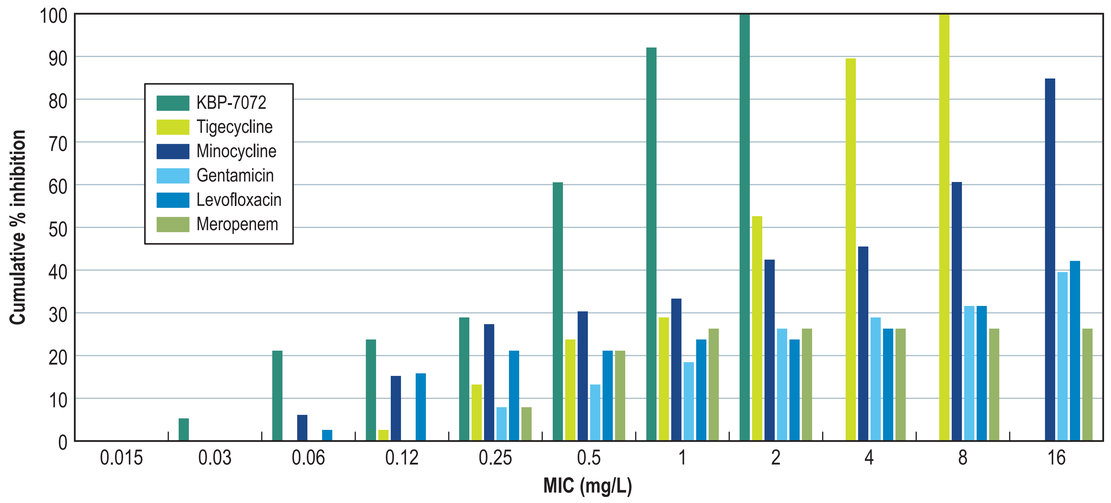

Table 1 Activity of KBP-7072 and comparators against 531 geographically diverse and molecularly characterized *A. baumannii* isolates

Antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	CLSI[a]			EUCAST[a]		
			%S	%I	%R	%S	%I	%R
KBP-7072 (531)	0.25	1	99.2[b]			100.0[b]		
Tigecycline (531)	1	4	79.5[c]	18.2	2.3	—		
Doxycycline (453)	1	>8	67.3	2.0	30.7	—		
Minocycline (454)	1	>8	73.8	6.8	19.4	—		
Tetracycline (457)	>8	>8	37.2	7.2	55.6	—		
Ceftazidime (531)	>16	>16	40.3	6.0	53.7	—		
Colistin (528)	≤0.5	1	92.8		7.2	92.8		7.2
Gentamicin (531)	8	>8	48.2	4.9	46.9	48.2		51.8
Levofloxacin (531)	>4	>4	39.5	2.8	57.6	37.9	1.3	60.8
Meropenem (531)	>8	>8	42.0	0.8	57.3	42.0	2.3	55.7

[a] Criteria as published by CLSI (2019) and EUCAST (2019).
[b] Percentage inhibited at ≤2 mg/L for comparison purposes only; highest MIC was 4 mg/L.
[c] Tigecycline FDA breakpoints for *Enterobacteriaceae* applied to *A. baumannii* for comparison purposes only.

Table 2 Activity of KBP-7072 and comparators against 38 colistin-R *A. baumannii* 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			
KBP-7072[b]	0 0.0	2 5.3	6 21.1	1 23.7	2 28.9	12 60.5	12 92.1	3 100.0							0.5	1
Doxycycline (n=33)		0 0.0	1 3.0	4 15.2	3 24.2	1 27.3	1 30.3	0 30.3	3 39.4	1 42.4				19 100.0	>8	>8
Minocycline (n=33)		0 0.0	2 6.1	3 15.2	4 27.3	1 30.3	1 33.3	3 42.4	1 45.5	5 60.6	8 84.8	5 100.0			8	32
Tetracycline (n=33)						0 0.0	2 6.1	3 15.2	2 21.2	2 27.3	1 30.3			23 100.0	>16	>16
Tigecycline			0 0.0	1 2.6	4 13.2	4 23.7	2 28.9	9 52.6	14 89.5	4 100.0					2	8
Ceftazidime							0 0.0	2 5.3	4 15.8	5 28.9	2 34.2	1 36.8		24 100.0	>32	>32
Gentamicin				0 0.0	3 7.9	2 13.2	2 18.4	3 26.3	1 28.9	1 31.6	3 39.5			23 100.0	>16	>16
Levofloxacin		0 0.0	1 2.6	5 15.8	2 21.1	0 21.1	1 23.7	0 23.7	1 26.3	2 31.6	4 42.1	8 63.2		14 100.0	32	>32
Meropenem				0 0.0	3 7.9	5 21.1	2 26.3	0 26.3	0 26.3	0 26.3	0 26.3	5 39.5		23 100.0	>32	>32
Piperacillin-tazobactam (n=36)		0 8.3	3 8.3	0 8.3	0 8.3	0 8.3	0 8.3	0 8.3	1 11.1	1 13.9	0 13.9	3 22.2	0 22.2	28 100.0	>128	>128

[a] MIC value is greater than the highest concentration tested.
[b] KBP-7072 MIC values ≤2 highlighted as susceptible for comparison purposes only.
[c] Tigecycline *Enterobacteriaceae* breakpoints applied to *A. baumannii* 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 KBP-7072 and comparators against 5 ESBL- and 5 MBL-producing *A. baumannii* isolates

Collection #	Category	MIC (mg/L)						Positive molecular tests
		KBP-7072	TGC[a]	CAZ	GM	LEV	MEM	
674334	ESBL	0.12	1	>32	≤1	>4	>8	**GES-22**, GES-like, OXA-23, OXA-51
689088	ESBL	0.06	0.5	>32	8	>4	>8	**GES-11**, GES-like, OXA-23, OXA-51
764370	ESBL	0.5	2	>32	>8	>4	>8	**CTX-M-15**, ADC-30, KPC-3, OXA-23, OXA-66, OXA-9, SHV-11, TEM-1
919444	ESBL	0.06	0.25	>32	>8	>4	>32	**CTX-M-115**, ADC-52-like, CARB-16, OXA-72, OXA-90, TEM-1
1003787	ESBL	0.06	0.5	>32	>16	>16	>32	**CTX-M-115**, ADC-52-like, CARB-16, OXA-72, OXA-90
143038	MBL	0.5	2	>16	>8	>4	>8	**IMP-1**
143675	MBL	0.5	2	>16	>8	>4	>8	**IMP-1**
177190	MBL	0.12	0.5	>16	≤2	>4	>8	**IMP-1**
602690	MBL	0.5	2	>32	>8	>4	>8	**NDM-1**, OXA-51, TEM-1
602847	MBL	1	2	>32	>8	>4	>8	**NDM-1**, OXA-23, OXA-51, TEM-1

[a] TGC, tigecycline; CAZ, ceftazidime; GM gentamicin; LEV, levofloxacin; MEM, meropenem; ESBL, extended-spectrum β-lactamase; MBL, metallo- β-lactamase.

Conclusions

- KBP-7072 ($MIC_{50/90}$, 0.25/1 mg/L; 99.2% inhibited at ≤2 mg/L) demonstrated potent *in vitro* activity against recent and molecularly characterized *A. baumannii* isolates, including isolates displaying resistance to colistin-R, ESBL-producing, and MBL-producing strains and outperformed all tetracycline-class comparators that included doxycycline, minocycline, tetracycline, and tigecycline
- KBP-7072 ($MIC_{50/90}$, 0.5/1 mg/L; 100.0% inhibited at ≤2 mg/L) was the most active compound tested against a subgroup of 38 recent colistin-R *A. baumannii* isolates, outperforming all tetracycline-class and comparator agents
- KBP-7072 inhibited all ESBL- and MBL-producing *A. baumannii* isolates at ≤0.5 mg/L and ≤1 mg/L, respectively
- These *in vitro* results support the continued development of KBP-7072 for the treatment of serious infections caused by susceptible and drug-resistant *A. baumannii* isolates

Acknowledgements

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