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In vitro Activity of Novel Compound RG6006 Against Clinical Isolates of *Acinetobacter baumannii-calcoaceticus* complex in the Presence of 20% Human Serum

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Introduction

- RG6006 is the first representative of a novel class of tethered macrocyclic peptide antibiotics active against *Acinetobacter* spp., including carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (ABC) organisms.
- ABC is often multidrug-resistant, presenting serious treatment challenges.
- In this study, we determined the *in vitro* activity of RG6006 against 100 isolates of ABC: 59 clinical isolates from the 2015–2018 SENTRY Antimicrobial Surveillance program and 41 isolates from the CDC Antimicrobial Resistance Bank.

Materials and Methods

- Clinical ABC isolates were collected from hospitalized patients in 50 medical centres from 26 countries.
- Susceptibility testing was performed using broth microdilution with cation-adjusted Mueller-Hinton broth (CAMHB) for the comparators colistin and meropenem.
  - The comparator breakpoints used CLSI/EUCAST (2022) criteria.
- RG6006 minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) were determined in CAMHB + 20% pooled human serum, both non-heat inactivated and heat-inactivated.

Results

- MIC distributions for RG6006 and its comparators plus MBC distributions for RG6006 for all isolates are shown in Table 1 and Figure 1.
- Isolates were mostly carbapenem-resistant, with 73% resistant to meropenem (CLSI/EUCAST). Susceptibility to colistin was 84.0% (EUCAST).
- MIC and MBC distributions for RG6006 and comparators against meropenem-resistant ABC are shown in Table 2, and colistin resistant isolates are shown in Table 3.
- RG6006 activity was not affected by colistin or meropenem resistance (Tables 2 and 3).
- RG6006 was active against ABC isolates, with $MIC_{50/90}$ values of 0.5/1 mg/L in both non-heat inactivated and heat-inactivated serum.
- 93% of isolates were inhibited by ≤1 mg/L, with an MIC range of ≤0.015–4 mg/L.
- The $MBC_{50/90}$ values of RG6006 were 1/4 mg/L in both non-heat inactivated and heat-inactivated serum.

Conclusions

- RG6006 tested in the presence of 20% human serum showed potent activity against a challenging set of ABC, including meropenem-resistant and colistin-resistant isolates.
- Activity was similar in non-heat inactivated serum compared to heat-inactivated serum, indicating that human complement does not contribute to compound activity.
- Accordingly, these *in vitro* results support the development of RG6006 as a treatment for infections caused by ABC, including carbapenem-resistant ABC.

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Table 1. Antimicrobial activity of RG6006 in various media, with comparators colistin, and meropenem tested against *Acinetobacter baumannii-calcoaceticus* complex isolates

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:													MIC_{50} or MBC_{50}	MIC_{90} or MBC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
Acinetobacter baumannii-calcoaceticus complex															
RG6006 in non-heat inactivated human serum MIC (100)	2 2.0		1 3.0	4 7.0	10 17.0	20 37.0	34 71.0	22 93.0	6 99.0	1 100					0.5	1
RG6006 in non-heat inactivated human serum MBC (100)	2 2.0		0 2.0	3 5.0	6 11.0	9 20.0	13 33.0	24 57.0	29 86.0	9 95.0	3 98.0	1 99.0	1 100		1	4
RG6006 in heat-inactivated human serum MIC (100)			0 0.0	4 4.0	11 15.0	21 36.0	34 70.0	23 93.0	5 98.0	2 100					0.5	1
RG6006 in heat-inactivated human serum MBC (100)			0 0.0	1 1.0	4 5.0	12 17.0	16 33.0	24 57.0	28 85.0	10 95.0	2 97.0	2 99.0	0 99.0	1 100	1	4
Colistin MIC (100)					0 0.0	27 27.0	43 70.0	9 79.0	**5** **84.0**	3 87.0	3 90.0	1 91.0	3 94.0	6 100	0.5	8
Meropenem MIC (100)				0 0.0	2 2.0	7 9.0	10 19.0	3 22.0	**5** **27.0**	1 28.0	0 28.0	4 32.0	7 39.0	61 100	>32	>32

Bold font indicates the CLSI intermediate and EUCAST susceptible breakpoint for colistin as well as the CLSI and EUCAST susceptible breakpoint for meropenem.
Abbreviations: MIC, minimal inhibitory concentration; MBC, minimal bactericidal concentration.

Table 2. Antimicrobial activity of RG6006 in various media, with comparators colistin, and meropenem tested against 72 meropenem resistant *Acinetobacter baumannii-calcoaceticus* complex isolates

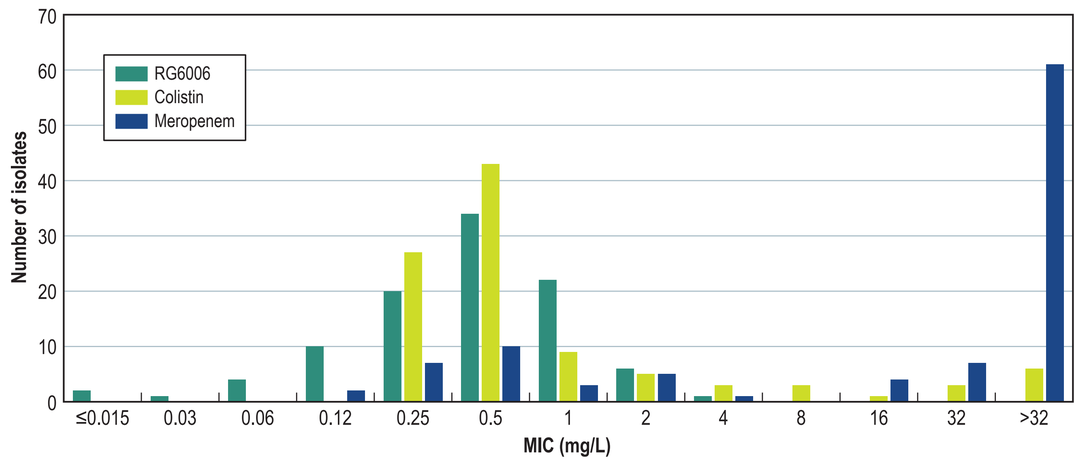
Antimicrobial Agent	No. and cumulative % of isolates inhibited at MIC (mg/L) of:													MIC_{50} or MBC_{50}	MIC_{90} or MBC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
RG6006 in Human Serum MIC (72)	2 2.8%	0 2.8%	1 4.2%	3 8.3%	13 26.4%	29 66.7%	18 91.7%	5 98.6%	1 100.0%					0.5	1
RG6006 in Human Serum MBC (72)	2 2.8%	0 2.8%	0 2.8%	0 2.8%	5 9.7%	10 23.6%	18 48.6%	24 81.9%	9 94.4%	2 97.2%	1 98.6%	1 100.0%		2	4
RG6006 in Heat-Inactivated Human Serum MIC (72)		0 0.0%	1 1.4%	4 6.9%	14 26.4%	27 63.9%	20 91.7%	4 97.2%	2 100.0%					0.5	1
RG6006 in Heat-Inactivated Human Serum MBC (72)			0 0.0%	1 1.4%	3 5.6%	12 22.2%	18 47.2%	25 81.9%	9 94.4%	2 97.2%	1 98.6%	0 98.6%	1 100.0%	2	4
Colistin MIC (72)				0 0.0%	19 26.4%	33 72.2%	7 81.9%	3 86.1%	2 88.9%	2 91.7%	0 91.7%	1 93.1%	5 100.0%	0.5	8
Meropenem MIC (72)										0 0.0%	4 5.6%	7 15.3%	61 100.0%	>32	>32

Abbreviations: MIC, minimal inhibitory concentration; MBC, minimal bactericidal concentration.

Table 3. Antimicrobial activity of RG6006 in various media, with comparators, colistin, and meropenem when tested in various media against 16 colistin-resistant *Acinetobacter baumannii-calcoaceticus* complex isolates

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:												MIC_{50} or MBC_{50}	MIC_{90} or MBC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
Colistin-resistant *Acinetobacter baumannii-calcoaceticus* species complex														
RG6006 in human serum MIC (16)	0 0.0	1 6.2	0 6.2	1 12.5	5 43.8	5 75.0	3 93.8	1 100.0					1	2
RG6006 in human serum MBC (16)	0 0.0	1 6.2	0 6.2	0 6.2	0 6.2	2 18.8	6 56.2	3 75.0	2 87.5	1 93.8	1 100.0		2	16
RG6006 in heat-inactivated human serum MIC (16)		0 0.0	1 6.2	1 12.5	5 43.8	5 75.0	2 87.5	2 100.0					1	4
RG6006 in heat-inactivated human serum MBC (16)		0 0.0	1 6.2	1 12.5	0 12.5	1 18.8	6 56.2	3 75.0	1 81.2	2 93.8	0 93.8	1 100.0	2	16
Colistin MIC (16)							0 0.0	3 18.8	3 37.5	1 43.8	3 62.5	6 100.0	32	>32
Meropenem MIC (16)		0 0.0	1 6.2	1 12.5	0 12.5	2 25.0	2 37.5	0 37.5	0 37.5	1 43.8	1 50.0	8 100.0	32	>32

Figure 1. Comparison of activities of RG6006, colistin, and meropenem against 100 *Acinetobacter baumannii-calcoaceticus* complex



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