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Antimicrobial activity of zosurabalpin against a diverse collection of aerobic and anaerobic bacterial and yeast isolates

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Introduction

- Antimicrobial resistance represents a critical threat to public health and safety.
- Addressing this challenge requires the development of novel antimicrobial agents aimed at pathogens identified on both the World Health Organization's priority pathogen list and the U.S. Centers for Disease Control and Prevention's urgent threat list, including carbapenem-resistant *Acinetobacter* species.
- Zosurabalpin (RG6006) is a novel tethered macrocyclic peptide antibiotic, currently in clinical development, which targets the $LptB_2FGC$ lipopolysaccharide transport and has demonstrated potent *in vitro* activity against antimicrobial resistant *Acinetobacter*; however, activity against adjacent bacterial and yeast species requires investigation.
- This study utilized Clinical and Laboratory Standards Institute (CLSI) reference susceptibility methodologies, including broth microdilution and agar dilution, to evaluate the *in vitro* activity of zosurabalpin and four standard of care comparator agents against a diverse collection of aerobic and anaerobic bacterial and yeast isolates.

Materials and Methods

- A total of 285 isolates recovered from 34 countries and documented infections during 2011–2023 were susceptibility tested against zosurabalpin (tested at 64–0.03 mg/L), meropenem, levofloxacin, fluconazole, and/or metronidazole using CLSI reference methods.
- Species identifications (ID) were determined by MALDI-TOF MS, except for *Shigella* and *Aeromonas* species that required DNA sequencing methods for species identification.
- Zosurabalpin was tested in cation-adjusted Mueller-Hinton broth (CAMHB) and was supplemented with 10% and 20% heat-inactivated horse serum (HoS) when testing *Acinetobacter* spp. isolates.
- Zosurabalpin MIC endpoints in CAMHB were determined at substantial reduction (SR) and complete inhibition of growth (100% read).

Results

- Zosurabalpin had potent activity against all *Acinetobacter* spp. isolates ($MIC_{50/90}$ values 0.12/1 mg/L; Table 2) in CAMHB read at SR; similar activity was observed when tested in CAMHB with 10% HoS and CAMHB with 20% HoS ($MIC_{50/90}$ values 0.25/1 mg/L).
- Zosurabalpin MIC values for *Acinetobacter* spp. isolates were considerably elevated when this agent was tested in CAMHB and read at 100% inhibition ($MIC_{50/90}$ values were 64/>64 mg/L).
- Of the 17 *Acinetobacter* spp. isolates tested (*A. baumannii-calcoaceticus* species complex [n=10], *A. johnsonii* [n=2], *A. junii* [n=2], and *A. lwoffii* [n=3]), 58.8% were susceptible to meropenem and levofloxacin by CLSI/EUCAST/FDA breakpoint criteria.
- Zosurabalpin was not active against the remaining Gram-positive aerobes, Gram-negative aerobes, anaerobes, and fungal isolates tested ($MIC_{50/90}$ values of >64/>64 mg/L) when read at both 100% inhibition and substantial reduction.

Conclusion

- Zosurabalpin had potent activity against all *Acinetobacter* spp. isolates, with close agreement observed when MICs were read using SR criteria in CAMHB and 10% and 20% heat-inactivated HoS supplemented CAMHB.
- Zosurabalpin displayed no activity against the remaining Gram-negative other than *Acinetobacter*, Gram-positive, anaerobe, and fungal isolates.
- These data demonstrate the *in vitro* activity of zosurabalpin against *Acinetobacter* isolates.

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Table. Antimicrobial activity of zosurabalpin and comparator agents against main organisms and organism groups when tested using broth microdilution and agar dilution susceptibility testing methods

Antimicrobial agent	MIC_{50}/ MIC_{90} value (mg/L)								
	Acinetobacter spp. (*n*=17)	Non-Fermenters (excluding *Acinetobacter*; *n*=68)	Anaerobe (*n*=30)	Enterobacterales (*n*=95)	Fastidious (*n*=16)	Staphylococci (*n*=25)	Streptococci (*n*=13)	Other Gram-Positive (*n*=19)	Yeast (*n*=2)
Zosurabalpin (0% HoS; 100% read)	64/>64	>64/>64	—	>64/>64	>64/>64	>64/>64	>64/>64	>64/>64	>64[a]
Zosurabalpin (0% HoS; SR read)	0.12/1	>64/>64	—	>64/>64	>64/>64	>64/>64	>64/>64	>64/>64	>64[a]
Zosurabalpin (10% HoS)	0.25/1	—	—	—	—	—	—	—	—
Zosurabalpin (20% HoS)	0.25/1	—	—	—	—	—	—	—	—
Zosurabalpin (0% HoS; agar)	—	—	>64/>64	—	—	—	—	—	—
Metronidazole (agar)	—	—	1/>64	—	—	—	—	—	—
Meropenem (agar)	—	—	0.12/1	—	—	—	—	—	—
Levofloxacin	0.12/>32	1/4	—	0.06/8	0.03/0.12	0.25/>32	1/1	1/>32	—
Meropenem	0.25/>32	0.5/>32	—	0.03/0.12	≤0.004/0.06	1/16	0.06/0.12	2/>32	—
Fluconazole	—	—	—	—	—	—	—	—	0.12[a]

Abbreviations: **HoS**, heat-inactivated horse serum; **MIC**, minimum inhibitory concentration; **SR**, substantial reduction.
[a] MIC values obtained for all yeast isolates tested (*n*=2)
Organisms included: ***Acinetobacter* spp. (*n*=17)** *A. baumannii-calcoaceticus* species complex (10), *A. johnsonii* (2), *A. junii* (2), *A. lwoffii* (3); **Non-Fermenters (*n*=68)** *Achromobacter insolitus* (5), *A. xylosoxidans* (5), *Aeromonas dhakensis* (2), *A. hydrophila* (5), *Alcaligenes faecalis* (10), *Burkholderia cepacia* species complex (10), *Chryseobacterium hominis* (1), *C. indologenes* (1), *Elizabethkingia meningoseptica/E. anophelis/E. miricola* (2), *Myroides injenensis* (1), *M. odoratimimus* (1), *Pseudomonas aeruginosa* (10), *Ralstonia mannitolilytica* (2), *Stenotrophomonas maltophilia* (10), unspeciated *Aeromonas* (3); **Anaerobe (*n*=30)** *Bifidobacterium breve* (1), *B. longum* (1), *Bacteroides fragilis* (4), *B. ovatus* (1), *Clostridium perfringens* (4), *C. ramosum* (3), *Cutibacterium acnes* (2), *Eggerthella lenta* (2), *Fusobacterium necrophorum* (1), *F. nucleatum* (1), *Parabacteroides distasonis* (1), *P. gordonii* (1), *Peptostreptococcus anaerobius* (2), *Porphyromonas asaccharolytica* (1), *P. somerae* (1), *Prevotella denticola* (1), *P. intermedia* (1), *Veillonella parvula* (2); **Enterobacterales (*n*=95)** *Citrobacter freundii* species complex (3), *C. koseri* (5), *Enterobacter cloacae* species complex (10), *Escherichia coli* (10), *Klebsiella aerogenes* (5), *K. oxytoca* (5), *K. pneumoniae* (10), *K. variicola* (5), *Morganella morganii* (3), *Pantoea agglomerans* (2), *Proteus mirabilis* (5), *P. vulgaris* (2), *Providencia rettgeri* (2), *P. stuartii* (2), *Raoultella ornithinolytica* (10), *Salmonella enterica* (2), *S. enterica* subsp. *enterica* serovar typhi (1), *S. enterica* subsp. *enterica* serovar typhimurium (1), *Serratia marcescens* (5), *Shigella boydii* (1), *S. flexneri* (3), *S. sonnei* (3); **Fastidious (*n*=16)** *Campylobacter coli* (1), *C. jejuni* (1), *Haemophilus influenzae* (2), *Moraxella catarrhalis* (10), *M. osloensis* (2); **Staphylococci (*n*=25)** *Staphylococcus aureus* (10), *S. capitis* (3), *S. epidermidis* (5), *S. haemolyticus* (2), *S. hominis* (3), *S. lugdunensis* (2); **Streptococci (*n*=13)** *Streptococcus agalactiae* (3), *S. mitis* group (3), *S. mitis/oralis* (2), *S. pneumoniae* (3), *S. pyogenes* (2); **Other Gram-Positive (*n*=19)** *Bacillus cereus* (2), *Enterococcus faecalis* (5), *E. faecium* (5), *Kocuria rhizophila* (2), *Lactobacillus plantarum* (2), *L. rhamnosus* (1), *Listeria monocytogenes* (2); **and Yeast (*n*=2)** *Candida albicans* (2).

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