

New Dual Inhibitors of Bacterial Topoisomerases with Broad-Spectrum Antibacterial Activity and In Vivo Efficacy against Vancomycin-Intermediate *Staphylococcus aureus*

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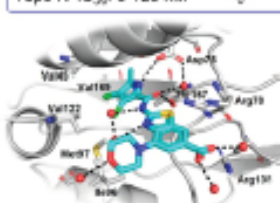
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ABSTRACT: A new series of dual low nanomolar benzothiazole inhibitors of bacterial DNA gyrase and topoisomerase IV were developed. The resulting compounds show excellent broad-spectrum antibacterial activities against Gram-positive *Enterococcus faecalis*, *Enterococcus faecium* and multidrug resistant (MDR) *Staphylococcus aureus* strains [best compound minimal inhibitory concentrations (MICs): range, <0.03125–0.25 µg/mL] and against the Gram-negatives *Acinetobacter baumannii* and *Klebsiella pneumoniae* (best compound MICs: range, 1–4 µg/mL). Lead compound 7a was identified with favorable solubility and plasma protein binding, good metabolic stability, selectivity for bacterial topoisomerases, and no toxicity issues. The crystal structure of 7a in complex with *Pseudomonas aeruginosa* GyrB24 revealed its binding mode at the ATP-binding site. Expanded profiling of 7a and 7h showed potent antibacterial activity against over 100 MDR and non-MDR strains of *A. baumannii* and several other Gram-positive and Gram-negative strains. Ultimately, in vivo efficacy of 7a in a mouse model of vancomycin-intermediate *S. aureus* thigh infection was also demonstrated.

Compound 7a
DNA gyrase IC₅₀: <10 nM
Topo IV IC₅₀: 8–120 nM

MIC (G+): <0.03125–0.25 µg/mL
MIC (G-): 0.5–16 µg/mL
S. aureus (VISA) MIC: <0.03125 µg/mL
A. baumannii MIC: 2 µg/mL (PDR, colistin-resistant)



in vivo efficacy
~ no in vitro toxicity
~ in vitro selectivity
~ in vitro and in vivo DMPK

INTRODUCTION

Due to the rapid emergence of drug-resistant bacteria, the post-antibiotic era has essentially begun, with fewer drugs being available for the successful treatment of many bacterial infections.^{1,2} Thus, in the 21st century, antimicrobial resistance (AMR) represents a major public health issue, and the World Health Organization (WHO) has listed AMR as one of the 10 biggest threats to global health.³ It is predicted that by 2050, AMR will cause at least 10 million deaths per year unless we successfully tackle this problem.⁴ In a recent review, it was estimated that 1.27 million deaths were directly attributable to antibacterial drug resistance in 2019 worldwide.⁵ The six leading pathogens contributing to the burden of AMR in 2019 were Gram-negative *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* and Gram-positive *Staphylococcus aureus* and *Streptococcus pneumoniae*.⁵ All have been included in the WHO's 2017 priority list of

pathogens for which new antibiotics are urgently needed and are also highlighted in CDC 2019 Antibiotic Resistance Threats Report.^{6,7} Methicillin-resistant *S. aureus* (MRSA) was identified as the leading pathogen responsible for the most deaths related to antibiotic resistance in 2019.⁵ MRSA mainly causes skin, soft tissue, bone and bloodstream infections, and it is the most common cause of postoperative wound infections. In many parts of the world, including Europe and the USA, the levels of community-acquired MRSA infections also tend to increase rapidly.^{8–11}

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