Three Novel Antibiotic Scaffolds for Treating Multidrug-resistant Gram-negative Infections

Rib-X Pharmaceuticals, Inc., New York, NY, USA

ABSTRACT

Objectives: To combat emerging multidrug-resistant (MDR) Gram-negative pathogens, including the Enterobacteriaceae featuring extended-spectrum beta-lactamases and carbapenemases such as KPC and NDM-1 as well as MDR Pseudomonas aeruginosa and Acinetobacter baumannii, bacteria strains, structure-based design was used to discover three new chemically novel scaffolds with a novel mechanism of inhibition of the large ribosomal subunit. The primary objectives of this effort were (1) demonstration that the novel scaffolds inhibited the translation machinery of the ribosome, (2) confirmation that the novel scaffolds were not affected by MLS resistance mechanisms and (3) optimization of these novel scaffolds across multiple vectors to afford compelling microbiological activity against a contemporary panel of clinical isolates of MDR Gram-negative.

Methods: Translation inhibition in wild-type and MLS-resistant Enterobacteriaceae ribosomes was measured as a surrogate for binding affinity. MLS-resistant bacterial strains were determined according to CLSI methods. Clinical isolates were obtained from Brigham and Women's Hospital.

Results: Translation IC₅₀ for all scaffolds were at the lower limit of detection, 20nM, against both wild-type and resistant E.coli ribosomes. Though the initial scaffolds showed little antibacterial activity, each was evolved to show consistent MICs of 4mg/l, against MDR Gram-positive and staphylococcus and MDR Pseudomonas aeruginosa Enterobacteriaceae, including E. coli and Klebsiella pneumoniae. Several subseries on these scaffolds showed promising potency against MDR P. aeruginosa and A. baumannii strains, with MIC ranges of 0.5 – 16 mg/l.

Conclusions: Design of three novel antibiotic scaffolds with a novel mechanism of inhibition was achieved. The scaffolds were evaluated along several chemical lines to yield multiple series with compelling activity against MDR Gram-postive and Gram-negative. Rational design against a compelling target can pave the way for completely new antibiotics to stay one step ahead of growing resistance.

INTRODUCTION

Increasing resistance to established antibacterial agents, coupled with a dwarfed pipeline, has diminished dramatically the useful antibacterial momentum over the last 20 years. Two key novel classes, targeting specific Gram-positive infections, have been introduced over this span, the oxazolidinones and the linezolid, having a variety of pharmacodynamic-positive mechanisms of action. These mechanisms are shown to be effective inhibitors of cell wall synthesis, as well as intercalating the bacterial cell membrane and thereby inhibiting bacterial growth through interfering with cell wall peptidoglycan synthesis.

METHODS