In vitro Antibacterial Activity of Novel Protein Synthesis Inhibitors Against Enterobacteriaceae

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Abstract

Background

Enterobacteriaceae are a family of bacteria that comprises a large number of species and it is concern in healthcare today. Antibiotics that have been used historically have lost their capacity to treat these difficult infections due to resistance. Several clinical isolates are resistant to multiple classes of antibiotics, and new antibiotic treatments are needed. Novel protein synthesis inhibitors are a class of drug that show promise for treatment of resistant infections. Our group has designed and synthesized a number of inhibitors that target the 30S ribosomal subunit.

Methods

In vitro. Bacterial isolates were previously frozen and stored at -80°C. Isolates were removed from the freezer and passaged on blood agar plates twice before testing. A 0.5 McFarland equivalent of each organism was prepared according to manufacturers’ specifications. Test compounds were prepared at 100x the highest final desired concentration and were serially diluted 2-fold in 96-well plates. An intermediate 10-fold dilution was prepared by adding 90 µL of 10 mM solution of DMSO to 10 µL of the 100x stock to achieve the 100x final desired concentration. The in vitro susceptibility was determined by the broth microdilution method (CLSI, Wayne, PA), and susceptibility of strains was determined against 100x of the final desired concentration. The MIC at 6 hr, and at 4x MIC at 8 hr.

Results

Table 1 - MIC values for E. coli ATCC 29245.

Table 2 - RX-04 compounds are highly potent against E. coli clinical isolates.

Table 3 - RX-04 compounds are active against Enterobacter spp. clinical isolates.

Table 4 - RX-04 compounds are highly potent against K. pneumoniae clinical isolates.

Conclusions

The three scaffolds of the RX-04 program, especially Scaffold P, demonstrate superior in-vitro activity against Enterobacteriaceae including drug-resistant isolates. In clinical isolates, MICs of these compounds were similarly lower than currently marketed drugs and MIC50/MIC90 values are similar, indicating that these compounds are not affected by mechanisms of resistance that limit other compounds. Bactericidal activity was observed in time-kill studies against E. coli, E. aerogenes, and K. pneumoniae, a result that can potentially apply for protein synthesis inhibitors. Overall, these novel protein synthesis inhibitors offer exciting potential for the treatment of difficult Gram-negative infections.

References


Figure 1. Compounds from the RX-04 class of Protein Synthesis Inhibitors.

Figure 2. Time-Kill Kinetics of E. coli

Figure 3. Time-Kill Kinetics of E. aerogenes

Figure 4. Time-Kill Kinetics of K. pneumoniae