Introduction

Bacterial resistance is increasing at an alarming rate in both hospital and community settings, which underscores an urgent need to develop new antibacterial agents. While current therapies is not expected. The primary objectives were: (1) demonstration of on-target activity, (2) confirmation that MLSb resistance mechanisms did not affect activity and (3) optimization along multiple vectors to afford compelling microbiological activity against contemporary MDR Gram-negative strains.

Methods

Establishing Antibacterial Activity

Scheme 1 - Synthesis of phenoxazinocytosine RX-B14

Results

Results suggest that the phenoxazinocytosine scaffold is a novel antibacterial core that can be elaborated to the desired final compounds in several straightforward steps. A number of chemically distinct classes of antibiotics including pleuromutilins, lincosamides, macrolides and aminoglycosides might be described herein.

Scope

Figure 1 - Crystal structures of a variety of antibiotics bound to the 50S subunit of Escherichia coli. Aset al., 2006. Curr Opin Struct Biol 16: 504–517.

Phenoxazinocytosines are novel antibacterial agents that are described herein. They bind near the peptidyl-transferase center, displaying similar but not identical interactions compared to chemically distinct classes of antibiotics including pleuromutilins, lincosamides, macrolides and aminoglycosides.

Conclusions

The 50S subunit of the ribosome is unique as a validated antibacterial target [3]. A number of chemically distinct classes of antibiotics including pleuromutilins, lincosamides, macrolides and aminoglycosides might be described herein.

Pharmacology

Phenoxazinocytosines (Scaffold B), will be described herein.

Figure 1 - Crystal structures of a variety of antibiotics bound to the 50S subunit of Escherichia coli. Aset al., 2006. Curr Opin Struct Biol 16: 504–517.


Antimicrobial Susceptibility Testing

For the purposes of evaluation, the standard broth microdilution method of the CLSI was used.

Table 1 - Initial Biological Activity for the Undecorated Phenoxazinocytosine

+---+---+---+---+---+---+---+---+---+---+
|   | Scaffold | RX-B10 | RX-B113 | RX-B168 | RX-B180 | RX-B114 | RX-B115 | RX-B116 | RX-B117 |
|---+---+---+---+---+---+---+---+---+---+---|
|   | M. abscessus | C. albicans | E. coli | K. pneumoniae | S. aureus | K. pneumoniae | A. baumannii | P. aeruginosa | E. coli | A. baumannii |
|---+---+---+---+---+---+---+---+---+---+---|
| CEF | 0.125 | 0.03 | 0.06 | 0.25 | 0.5 | 2 | 0.03 | 2 | 0.06 | 0.03 |
| CIP | 0.03 | 0.015 | 0.25 | 0.25 | 0.03 | 2 | 0.125 | 16 | 0.5 | 1 |
| IMP | 0.25 | 0.25 | 4 | 4 | 0.25 | 4 | 0.5 | 4 | 4 | 4 |
| TET | 0.125 | 0.125 | 0.25 | 0.25 | 0.125 | 0.25 | 0.125 | 0.25 | 0.125 | 0.125 |

References
