SAR of 11, 12-Carbamate Macrolides/Ketolides Linked With 1,4-Substituted-[1,2,3]-Triazoles

C Hwang, J Duffield, Y Chiu, C Liang, S Yao, N Roberts, F Babakhani, P Sears, Y Shue, Y Ichikawa, P Fernandes, D Pereira, A Romero

Background:

Structural features associated with ketolide antibiotics that may improve activity over their macrolide predecessors typically include: (1) lack of the 3-*O*-cladinose (2) presence of 3-keto group (3) the presence of heterocyte tethered to 11, 12-carbamate that interacts specifically with domain II of the bacterial rRNA. A novel compound library was designed to optimize domain II binding and antibacterial activity by the incorporation of the chemically robust [1,2,3]-triazole group.

Methods:

The regio-selective and complete syntheses of these compounds are presented for variety of substituted triazoles with varying linker lengths illustrated. Primary screening panel consisted of relevant *Staph. aureus*, *S. pyogenes*, *S. pneumoniae* (including strains resistant to azithromycin and telithromycin). MICs against all pathogens were determined using broth micro-dilution method as per NCCLS guidelines.

Results:

CEM-101 was found to be highly potent having MICs against *S. pneumoniae* (3773) of ≤ 0.125 µg/mL and *S. pyogenes* (1850) of 0.5 µg/mL, compared to 1 and 8 µg/mL, respectively for Telithromycin. CEM-103, an analogue of CEM-101 contains the 3-*O*-cladinose was found to be less active. Non-heteroaromatic substituted triazole containing ketolides were less active.

Conclusions:

A novel ketolide synthetic approach was investigated whereby chemically robust substituted triazole groups were incorporated regio-selectively into the 11, 12-carbamate side chain. Within this new and unique triazole containing macrolide class, the SAR suggested key essential structural features: 1) [1,2,3]-triazole ring substituted at the 4-position with a heteroaromatic ring 2) butyl linker was an optimal length of the triazole side chain 3) 3-keto group. CEM-101 incorporated all of these structural attributes resulting in excellent antibacterial activity.