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.