Clarithromycin is a macrolide antibiotic active against Gram-positive bacteria. The target is the bacterial ribosome where the antibiotic is inhibiting protein biosynthesis. We focus on the glycan as it was shown to induce resistance. However, if the cladinosyl moiety of clarithromycin is removed, antibiotic activity is significantly reduced [1,2]. Herein, we present a semisynthetic approach to not only regenerate antimicrobial activity but to break and bypass resistance mechanisms. Importantly, some of our macrolides show antimicrobial activity against the Gram-negative ESKAPE pathogen \textit{A. baumannii}, which is fully resistant to known macrolides.

Starting with clarithromycin, we synthesized a series of novel macrolides, by replacing the cladinosyl moiety with selected aryl acetic acid moieties at the C3-position of the macrolide skeleton [1]. Additionally, 11,12-carbamate acylides and substituted 11,12-N-alkyl-heteroaryl-carbamate acylides were synthetically assembled to study synergistic effects and further improve antibiotic activity.

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