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Design, Synthesis and Structure-bactericidal Activity Relationships of Novel 9-Oxime Ketolides and Reductive Epimers of Acylides

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Abstract: Erythromycin was long viewed as a bacteriostatic agent. The erythromycin derivatives, 9-oxime ketolides have a species-specific bactericidal profile. Among them, the 3'-allyl version of the 9-oxime ketolide **1** (Ar = 3-quinolyl; **17a**) is bactericidal against *Streptococcus pneumoniae* and *Streptococcus pyogenes*. In contrast, the 2-fluoro analogs of **1**, **13a** (Ar = 3-quinolyl), **13b** (Ar = 6-quinolyl) and **24a** (Ar = 4-isoquinolyl), show bactericidal activities against *S. pneumoniae*, *Staphylococcus aureus* and *Moraxella catarrhalis*, while the 2-fluoro analogs **13c** (Ar = 3-aminopyridyl) and **24b** (Ar = 3-carbamoylpyridyl) are only bactericidal against *S. pneumoniae* and *Haemophilus influenzae*. Reduction of the ketolides led to novel epiacylides, the 3-*O*-epimers of the acylides. Alteration of linker length (**30b** vs. **30a**), 2-fluorination (**33** vs. **30a**) and incorporation of additional spacers at the 9-oxime or 6-OH (**35**, **40** vs. **30a**) did not restore the epiacylides back to be as active as the acylide **31**. Molecular docking suggested that epimerization at the 3-position reshapes the orientation of the 3-*O*-sidechain and leads to considerably weaker binding with bacterial ribosomes.

Keywords: Erythromycin; Community-acquired bacterial pneumonia; Bactericidal activity; Ketolide; Acylide; Epimer

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