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

Jing-Chao Tian, Xu Han, Wei Lv, Ya-Xin Li, Hui Wang, Bing-Zhi Fan, Mark Cushman, Jian-Hua Liang

PII: S0960-894X(17)30175-0
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.02.041
Reference: BMCL 24713

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 26 December 2016
Revised Date: 15 February 2017
Accepted Date: 17 February 2017

Please cite this article as: Tian, J-C., Han, X., Lv, W., Li, Y-X., Wang, H., Fan, B-Z., Cushman, M., Liang, J-H., Design, Synthesis and Structure-bactericidal Activity Relationships of Novel 9-Oxime Ketolides and Reductive Epimers of Acylides, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.02.041

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

Jing-Chao Tian,[a] Xu Han,[a] Wei Lv,[b] Ya-Xin Li,[a] Hui Wang,[c]

Bing-Zhi Fan,[a] Mark Cushman,[b] Jian-Hua Liang[a,*]

[a]School of Life Science, Beijing Institute of Technology, Beijing 100081, China

[b]Department of Medicinal Chemistry and Molecular Pharmacology, College of Pharmacy, and the Purdue Center for Cancer Research, Purdue University 47907 USA

[c]Biomedical School, Beijing City University, Beijing 100094, China

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

*To whom correspondence should be addressed. J.-H. Liang: Tel: 86-10-68912140, Email: ljhbit@bit.edu.cn.