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**Abstract**

Macrolides accumulate inside eukaryotic cells, which has been considered advantageous for the treatment of intracellular infections. CEM-101, a novel fluoroketolide with a 11,12-carbamate-butyl-[1,2,3]-triazolyl-phenylamino sidechain, demonstrates enhanced potency compared to telithromycin. We have assessed the cellular accumulation and intracellular activity of CEM-101 towards the intracellular forms of Staphylococcus aureus, Listeria monocytogenes, and Legionella pneumophila in comparison with azithromycin (AZM) or clarithromycin (CLR) in THP-1 cells.

**Methods:**

- **All experiments were performed with the human macrophage cell line THP-1.** Drug accumulation was measured by flow cytometry. Intracellular activity was tested in broth or in THP-1 macrophages.
- **Azithromycin and clarithromycin** were used as comparators in uninfected cells at 37°C (Ce=10 mg/L).
- **THP-1 cells** were infected at MOI 0.1 (strain ATCC 33153) and incubated with azithromycin or clarithromycin for 48 h.

**Results:**

- **CEM-101 markedly accumulates in THP-1 macrophages by a proton-dependent mechanism and is not subject to P-gp efflux.**
- **CEM-101 showed significantly greater potency against phagocytosed S. aureus, L. monocytogenes, and L. pneumophila, which is entirely attributable to its lower MIC but not to its accumulation.**
- **CEM-101 should show enhanced in vivo potency if used at doses similar to those of the comparators tested here.**

**Conclusions:**

- CEM-101 shows improved activity compared to the parent compound (4). Together with the removal of the cladinose, this led to the discovery and development of the tetracyclic fluoroketolide CEM-101 containing an 11,12-carbamate-butyl-[1,2,3]-triazolyl-aminophenyl sidechain (see structure underneath) that shows enhanced potency sidechain (see structure underneath) that shows enhanced potency compared to telithromycin (6).

**References**

4. Broth THP-1 macrophages with telithromycin (10 μg/mL) and clarithromycin (10 μg/mL). Programmed cell death (TUNEL assay).
5. Cell viability and apoptosis of THP-1 macrophages. Cell viability was assessed using the mitochondrial activity assay 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) (35).
6. **CEM-101 should show enhanced in vivo potency if used at doses similar to those of the comparators tested here.**

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