Dichalcogenide Fidaxomicin Derivatives to Probe Thiol-Mediated Uptake into Bacteria

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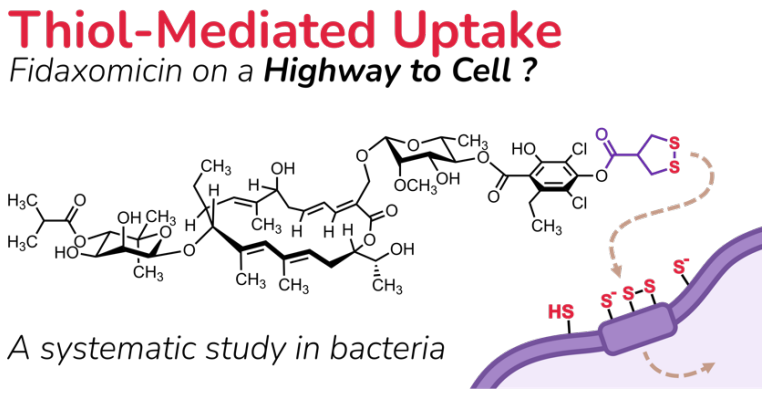
The natural product fidaxomicin (Fdx) is a narrow-spectrum antibiotic clinically prescribed for the treatment of *Clostrodioides difficile* infections. However, limited cellular uptake reduces its therapeutic potential, particularly against Gram-negative bacteria and mycobacteria. In this study, we investigated Thiol-Mediated Uptake (TMU)[2] to promote the delivery of Fdx into bacterial cells. We synthesized a library of Fdx derivatives bearing cyclic dichalcogenide moieties, and evaluated their antimicrobial properties against *C. difficile* and *Mycobacterium tuberculosis*. Remarkably, the synthetic Fdx derivatives retained strong levels of antibacterial activity, and the disulfide-containing analogs outperformed their all-carbon control counterparts in many instances. We then developed a systematic study to investigate the mechanistic impact of the introduced disulfide functionalities by conducting experiments with TMU inhibitors, and quantifying intracellular accumulation in *Mycobacterium bovis* BCG, a model organism for *M. tuberculosis,* via LC-MS/MS. While complete disentanglement of the factors influencing activity was not feasible, features such as compound stability and lipophilicity were identified as significant contributors. Overall, the superior performance of disulfide analogs suggests that differences in cellular entry or intracellular processing, potentially related to TMU, are involved. This work highlights that TMU remains a viable approach for modulating uptake of therapeutic agents into bacterial cells.



[1] A. Kraimps, T. Griesser, R. Wang, S. Dittman, J. Costafrolaz, E. Jung, P. H. Viollier, S. Sievers, P. Sander, K. Gademann, **2025**, doi:10.26434/chemrxiv-2025-81f96

[2] Q. Laurent, R. Martinent, B. Lim, A.-T. Pham, T. Kato, J. López-Andarias, N. Sakai, S. Matile, *JACS Au* **2021**, 1, *6*, 710–728