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Our research group focuses on generating new chemical classes of antibiotics for the treatment of Gram-negative infections. The main challenge in this area of research is finding molecules that bypass the permeability barrier created by the outer membrane and efflux pumps. Historically, molecules identified from fragment-based or high-throughput screens have been difficult to optimize simultaneously for on-target cellular activity, favorable bacterial permeability properties, and the chemical properties required of a safe and efficacious antibiotic. A major focus of our research is to understand the chemical basis for bacterial permeability and use that information to drive the optimization of novel antibiotics. There are only a few mechanisms by which small molecules are thought to enter Gram-negative cells: porin-mediated diffusion, active transport, and facilitated uptake via membrane permeabilization. Though examples of each are well-documented, the molecular bases for these processes are not completely understood. We would like to develop approaches to chemically probe these permeation mechanisms, such as by synthesizing hybrids of known permeable antibiotics and impermeable “cargo” moieties, or by directly and selectively perturbing the proteins that mediate permeation. Our medicinal chemistry group works at the scientific interface between chemistry and biology, supporting the development of novel orthogonal approaches that can drive the rational design of novel antibiotics. Chemistry is carried out in state-of-the-art organic synthesis laboratories with automated analytical and purification processes. Newly-synthesized molecules will be characterized using a comprehensive suite of approaches, including biochemical, genetic, and cellular assays.

Selected Publications

Optimization of physicochemical properties and safety profile of novel bacterial topoisomerase type II inhibitors (NBTIs) with activity against Pseudomonas aeruginosa.
Reck F, Ehmann D, Dougherty T, Newman J, Hopkins S, Stone G, Agrawal N, Ciaccio P, McNulty J, Baarthlow H, O’Donnell J, Goteti K, Breen J, Comita-Prevoir J, Cornebise M, Cronin M, Eyermann CJ, Geng B, Carr G, Pandarinathan L, Tang X, Cottone A, Zhao L, Bezdenejnih-Snyder N.

Bioorganic & Medicinal Chemistry. 2014; 22: 5392-5409.

Novel substituted (pyridin-3-yl)phenyloxazolidinones: antibacterial agents with reduced activity against monoamine oxidase A and increased solubility
Reck F, Zhou F, Eyermann CJ, Kern G, Carcanague D, Ioannidis G, Illingworth R, Poon G, Gravestock MB.
Journal of Medicinal Chemistry. 2007; 50(20): 4868-4881.

Inhibitors of the bacterial cell wall biosynthesis enzyme MurC.
Reck F, Marmor S, Fisher S, Wuonola MA.
Bioorganic Medicinal Chemistry Letters. 2001; 11: 1451-1454.

Click here for additional publications.

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