The Synthesis of Novel Agents Targeting *Salmonella enterica* Typhimurium

Jake Schmitt, Jason West, Brian Ahmer, Mark Mitton-Fry**
[1]College of Pharmacy - Medicinal Chemistry and Pharmacognosy, The Ohio State University

Foodborne illness resulting from non-typhoidal *Salmonella enterica* is a major contributor to global diarrheal diseases[1], with the potential to induce life-threatening morbidity within afflicted patients. In addition to its widespread impact, *S. enterica* has developed significant antimicrobial resistance, challenging the efficacy of current antibiotics. Through high-throughput screening (HTS), a promising hit compound was identified as an inhibitor of a unique Fructose-Asparagine (F-Asn) metabolic pathway utilized by *S. enterica*. This pathway converts F-Asn into Glucose-6-Phosphate (G6P) through a multi-step pathway involving several enzymes, including FraB[2]. Inhibiting FraB leads to cell death due to the accumulation of a toxic intermediate, 6-Phosphofructose-Aspartate (6-P-F-Asp). Building upon the original hit scaffold, an extensive exploration of structure-activity relationships (SAR) has been undertaken in an attempt to enhance the potency of the original hit and create a novel narrow-spectrum antibiotic. The original hit offers a multitude of functionality that can be easily modified to explore the SAR, which allowed for the synthesis of 26 unique derivatives. While the SAR panel may not have yielded significantly more potent compounds, ongoing HTS efforts explore alternative chemical cores to effectively inhibit this crucial metabolic pathway.

[1] "Salmonella (Non-Typhoidal)." World Health Organization, World Health Organization, www.who.int/news-room/fact-sheets/detail/salmonella-(non-typhoidal). Accessed 26 Sept. 2023.

[2] Sabag-Daigle, A., Blunk, H., Sengupta, A. et al. A metabolic intermediate of the fructose asparagine utilization pathway inhibits growth of a Salmonella fraB mutant. Sci Rep 6, 28117 (2016). https://doi.org/10.1038/srep28117