From Gram Positives to Gram Negatives: Discovery of Novel Aryloxazolidinone-Linked Bacterial Topoisomerase Inhibitors (NBTIs)

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The emergence of infections caused by multidrug-resistant Gram-negative organisms is one of the biggest threats to global health today. While many bacterial infections are becoming increasingly untreatable large pharmaceutical companies have left the field. As a result, the approval of novel and more effective antibiotics has been dramatically declining over the last decades.

Bacterial topoisomerases, such as DNA Gyrase and Topoisomerase IV, are important antibacterial targets and several classes of inhibitors were discovered in the past, but only the fluoroquinolones (FQs) became clinically successful. Unfortunately, their utility has been significantly compromised due to emerging resistance. Over the last years compounds of a novel class of bacterial topoisomerase inhibitors (NBTIs) devoid of cross-resistance with FQs have advanced to clinical stage. However, despite promising properties the latter show no significant activity against the most problematic Gram-negative pathogens, particularly against *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*.

Presented herein are the discovery and characterization of novel aryloxazolidinone-linked bacterial topoisomerase inhibitors (NBTIs) representing a new chemical class with potent broad-spectrum antibacterial activity, including the most difficult-to-treat multidrug-resistant Gram-negative bacteria. Compounds with Gram-negative whole cell activity could be designed by improving target potency and increasing intracellular accumulation.