Targeting LpxH in Lipid A Biosynthesis: A Novel Strategy Against Multidrug-Resistant Gram-Negative Pathogens

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The alarming rise of Gram-negative nosocomial pathogens resistant to nearly all available antibiotics poses a critical challenge to effective patient care. Although recent FDA approvals have expanded the arsenal, most new agents primarily target drug-resistant Gram-positive bacteria. As a result, there is an urgent need for novel antibiotics that exploit uncharted pathways to counter the escalating public health threat of multidrug-resistant Gram-negative infections.

Leveraging structure- and dynamics-based ligand design and optimization, we have developed a new series of sulfonyl piperazine inhibitors targeting LpxH, an essential enzyme in lipid A biosynthesis, as promising antibiotics against multidrug-resistant Enterobacterales. Current efforts are focused on identifying a lead LpxH inhibitor with potent activity against *Escherichia coli* and *Klebsiella pneumoniae*, alongside comprehensive evaluation of its safety and efficacy in murine infection models. Successful completion of these studies will validate the therapeutic potential of LpxH-targeting antibiotics and lay the groundwork for accelerated clinical development.