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Poster abstract submission

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Poster title

First-in-class, ultra-narrow spectrum antibacterial with a novel mode of action against multidrug-resistant Neisseria gonorrhoeae

Poster abstract

Gonorrhea is a major sexually transmitted disease, affecting approximately 80 million people annually. The emergence of multi-drug resistant (MDR) Neisseria gonorrhoeae has caused many frontline antibiotics to be ineffective, creating an urgent need for novel therapeutic classes. By exploring the chemical inventory of competitive bacterial interactions, we identified 2-nonyl-4-quinolone N-oxide (NQNO), a secondary metabolite produced by Pseudomonas aeruginosa, which exhibits unprecedented selectivity against N. gonorrhoeae.

Our study demonstrates that NQNO possesses exceptional efficacy against the pathogen, including the multidrug-resistant gonococcal strains. Strikingly, NQNO remains inactive against commensal Neisseria species, vaginal Lactobacilli, and other mucosal microbes. Crucially, the compound showed no toxicity against human cells and demonstrated an acceptable safety profile across all tests. Mechanistic studies revealed a unique mode of action: NQNO disrupts the gonococcal electron transport chain (ETC), leading to ATP/NADH depletions and increased oxidative stress, which subsequently triggers the release of the endogenous Zeta1 toxin.

Structure-activity relationship (SAR) optimization led to the development of NQNO derivatives with low nanomolar potency, bactericidal activity, and lack of resistance development. In a humanized mouse model of vaginal infection, topical applications of NQNO-derived compounds successfully eradicated the pathogen. These findings introduce a novel strategy for selectively targeting N. gonorrhoeae by exploiting the electron transport chain, paving the way for the development of an ultra-narrow-spectrum antibiotic to combat multidrug-resistant gonococci.

Research topic Small molecule therapeutics

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