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In Vivo Activity Profiling of Biosynthetic Darobactin D22 Against Critical Gram-negative Pathogens

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During recent years, the naturally occurring darobactins have emerged as a promising compound class to combat infections caused by critical Gram-negative pathogens (Imai *et al.* 2019, Kaur *et al.* 2019). Using biosynthetic approaches, we developed the non-natural darobactin analogue D22 with significantly improved antibacterial activity compared to the naturally occurring darobactin A (Seyfert *et al.* 2022, WO2022/175443). We recently demonstrated *in vivo* activity of D22 against key critical Gram-negative human pathogens (Kany *et al.*, 2024), as shown *e.g.* in murine models of *Escherichia coli* peritonitis and urinary tract infection (UTI). Furthermore, we observed restored survival of *Acinetobacter baumannii*-infected embryos in a zebrafish infection model. These *in vivo* proof of concepts (PoC) in diverse models of infection against highly relevant pathogens, including drug-resistant isolates, highlight the versatility of darobactins in the treatment of bacterial infections and show superiority of D22 over the natural darobactin A. Together with a favorable safety profile, these findings pave the way for further optimization of the darobactin scaffold towards the development of a novel antibiotic.

References

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