

# PENICILLIN-BASED SULFONE-SIDEROPHORE CONJUGATES FOR RESTORING $\beta$ -LACTAM ANTIBIOTIC EFFICACY IN MULTIDRUG-RESISTANT BACTERIA

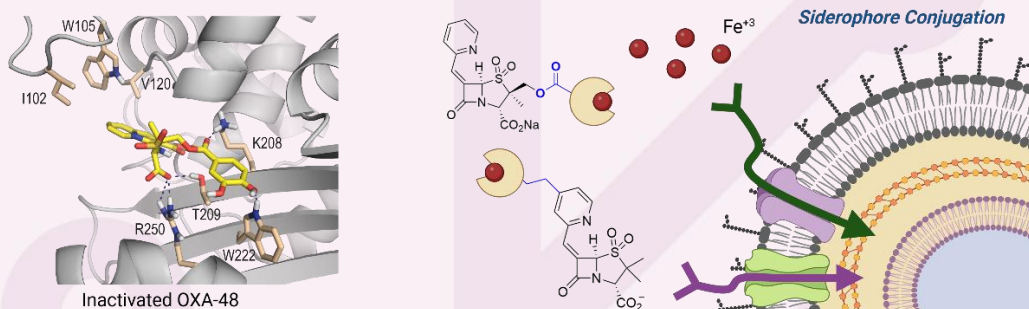
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Membrane permeability serves as a natural defense barrier that contributes to increased drug resistance in bacteria, particularly among Gram-negative pathogens. Consequently, the accurate delivery of antibacterial agents to their intracellular targets has become a key area of research in infectious disease therapeutics, aiming to improve drug efficacy. Although efficient cytosolic transport of siderophore–antibiotic conjugates remain challenging, significant progress has been made in delivering  $\beta$ -lactam antibiotics to the periplasmic space via bacterial iron uptake pathways.<sup>1</sup> A notable example is cefiderocol, the first siderophore–cephalosporin conjugate approved by the U.S. Food and Drug Administration. These conjugation strategies have also been extended to the targeted delivery of  $\beta$ -lactamase inhibitors, such as the penicillin-based sulfone compound, to restore  $\beta$ -lactam antibiotic efficacy against multidrug-resistant bacteria.<sup>2,3</sup> A series of derivatives functionalized with diverse iron chelators and linkages to the penicillin scaffold were synthesized and evaluated *in vitro*.<sup>4</sup> The results on the ability of these compounds to restore  $\beta$ -lactam antibiotic efficacy in difficult-to-treat bacterial pathogens that produce various  $\beta$ -lactamase enzymes, along with kinetic studies with the isolated enzymes, allowed us to identify a novel  $\beta$ -lactamase inhibitor with an expanded spectrum of activity. Molecular dynamics simulation studies provided us with further information regarding the molecular basis of the relative inhibitory properties of the most relevant compound described herein.<sup>5</sup>



## References:

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- (5) Financial support by the Spanish State Agency of Research (PID2022-136963OB-I00/AEI/10.13039/501100011033), the Xunta de Galicia [ED431C 2025/05 and Centro singular de investigación de Galicia accreditation 2024-2027 (ED431G 2023/03)], and the European Regional Development Fund is acknowledged.