Alistair Farley
Department of Chemistry
INEOS Oxford Institute
University of Oxford

Title: Imitation of β-lactam binding enables broad-spectrum metallo-β-lactamase inhibitors

Abstract:
Carbapenems are vital antibiotics, but their efficacy is increasingly compromised by metallo-β-lactamases (MBLs). We report the discovery and optimization of potent broad-spectrum MBL inhibitors. A high-throughput screen for NDM-1 inhibitors identified indole-2-carboxylates (InCs) as potential β-lactamase stable β-lactam mimics. Subsequent structure–activity relationship studies revealed InCs as a new class of potent MBL inhibitor, active against all MBL classes of major clinical relevance. Crystallographic studies revealed a binding mode of the InCs to MBLs that, in some regards, mimics that predicted for intact carbapenems, including with respect to maintenance of the Zn(II)-bound hydroxyl, and in other regards mimics binding observed in MBL–carbapenem product complexes. InCs restore carbapenem activity against multiple drug-resistant Gram-negative bacteria and have a low frequency of resistance. InCs also have a good in vivo safety profile, and when combined with meropenem show a strong in vivo efficacy in peritonitis and thigh mouse infection models.