New Generation of Penicillin-binding-proteins and β-lactamase Inhibitors

Main supervisor: Prof Chris Schofield, Chemistry Research Laboratory, University of Oxford
Co-supervisor: Prof Christopher Dowson, School of Life Sciences, University of Warwick
Host institution: University of Oxford

Project description:
This project will involve the design and synthesis of new types of inhibitor inspired by the mode of action of β-lactams, but which are insensitive to resistance mediated by β-lactamases. It will build upon (i) extensive structural/biophysical analyses employing both solution and crystallographic methods, (ii) developing mechanistic work on PBPs and β-lactamases, (iii) work extending over several decades aimed to developing new types of PBP and β-lactamase inhibitor working either via acylation or as ‘transition state’ analogues (see e.g., ACIE, Angew. Chem. Int. Ed, 2017, 56, 3862; Chemical Science, 2017, 8, 928; Nature Communications, 2016, 7, 12406). The student will extend this work by developing boronates and other types of inhibitor which mimic high energy intermediates in PBP catalysis (identified via collaborative work with the Dowson group in Warwick). The work will involve both design of compounds via analysis of crystallographic data, synthesis of compounds and depening on the interests of the student involvement in assays and solution based biophysical analyses employing techniques such as NMR and SPR. The project will provide training in cutting edge synthetic and chemical biology techniques. The successful candidate will be also able to undertake additional training opportunities and local student cohort activities available to MRC or EPSRC Doctoral Training Programme students.

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