

## Simulation-led engineering of Diels-Alderase activity and selectivity for sustainable biosynthesis of new antibiotics

### Supervisory team:

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**Host institution:** University of Bristol

### Project description:

Enzymes are remarkable biocatalysts that allow rapid, selective and efficient catalysis under mild conditions. Biotechnology exploits the rate-enhancing properties of these natural biocatalysts to manufacture high added-value products. Of particular current interest are enzymes that catalyse the Diels-Alder reaction, a [4+2] cycloaddition reaction widely recognised as one of the cornerstone synthetic organic reactions of the 20th century. It is commonly employed in the synthesis of bioactive natural products, including numerous important pharmaceuticals. Without enzyme biocatalysts, harsh reaction conditions (high temperature, high pressure) often must be employed, and precise control over the product outcome is limited. Enzymes that catalyse this reaction, Diels-Alderases, are therefore highly attractive.

In this project, the focus will be on Diels-Alderases involved in the biosynthesis of tetronate antibiotics such as abyssomicins, natural products with highly promising antibiotic activity. We have already established the structure and mechanism of two of these in detail, for which computational simulation, including docking, molecular dynamics and QM/MM reaction simulations, has proven highly valuable. The same is true for crucial tailoring enzymes that are required before and after the Diels-Alderase step to arrive at the active polyketide-based antibiotic. The project aims to use these techniques in new computational prediction protocols that can suggest enzyme variants with desired changes in activity and specificity, for example to obtain tetronate antibiotics with improved characteristics for pharmaceutical use. To test and improve these predictions, experimental characterisation of promising enzyme variants (product outcome, kinetics and structural biology) will be performed. By working with our industrial partner AstraZeneca, the impact of engineered enzymes can be realised by testing their use for generating valuable building blocks and scaffolds for pharmaceutical drug discovery. This interdisciplinary project combines the expertise in computational simulation of enzymes in Bristol and the expertise from an internationally leading academic team with multidisciplinary expertise of polyketide natural product biosynthesis and relevant experimental techniques (enzymology, molecular biology, chemistry and structural biology).

Combining simulation and experiment in this way is still developing, but will become increasingly important; in Bristol, we are at the forefront of this development. The multidisciplinary environment ensures the student will acquire a range of skills that will arm them for a future career in academic or industrial bioscience (including pharmaceutical science). The student will be embedded in the vibrant research environment in Bristol, including the Centre for Computational Chemistry and the Bristol BioDesign institute, ensuring a wide range of interactions, seminar programmes and courses.

**Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.**