Fungal Natural Products: Engineering Biosynthetic Pathways to Deliver Novel Bioactive Compounds

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Project description:

Natural products research plays a vital role in scientific endeavour leading to novel bioactive compounds for use in crop science and the pharmaceutical industry. Exploration of fungal cultures has been particularly fruitful in the discovery of key pharmaceuticals such as antibiotics (penicillin) and cholesterol lowering drugs (lovastatin) as well as leads in agriculture (e.g. strobilurin, an inspiration for the commercially important antifungal compound azoxystrobin). In addition, biosynthetic studies on fungal natural products are providing fascinating insights into genetics and enzymology with the prospect of manipulating pathways to provide new bioactive products cleanly and efficiently.

This project will focus on the maleidrides, an important family of polyketide-derived natural products characterised by a medium-sized alicyclic ring with one or two fused maleic anhydride moieties e.g. byssochlamic acid (a nonadride assembled on a 9-membered ring core) and zopfiellin, an octadride (with an 8-membered central ring). They exhibit important bioactivities e.g. rubratoxin A has the potential to enhance anticancer immunity leading to tumour regression and cornexistin, a selective herbicide, inhibits the growth of weeds, but is not harmful to maize crops.

The maleidrides are biosynthesised via fascinating pathways which include regiochemical dimerisation reactions, controlled by the same unique set of maleidride enzymes (Angew. Chem. Int. Ed, 2016, 55, 6784). Initial variation is introduced by differing monomer chain lengths and saturation level, controlled by highly reducing polyketide synthases. Multiple dimerisation modes lead to diversity in the core primary maleidride cyclic structure, which then undergoes further tailoring, increasing the complexity of the mature compound. Tailoring reactions can include hydroxylation, gamma-hydroxybutenolide generation, and ring contraction. We will screen maleidride producing fungi to characterise their biosynthetic genes. Key steps in their biosynthetic pathways will be elucidated (e.g. the fascinating mechanism of ring contraction, Chem Sci, 2020, 11, 11570). A library of novel compounds will be generated using a range of techniques including gene knock-out, heterologous expression, biotransformations and late-stage chemical functionalisation and their bioactivities will be assessed.

This interdisciplinary project will combine a range of state-of-the-art techniques at the chemistry-biology interface with expertise from an internationally leading academic team and co-workers. The research will be part of a larger collaborative program in Bristol which includes structural biology, enzymology, molecular biology, computational simulations, synthesis, isotopic labelling and structure elucidation using spectroscopic techniques.