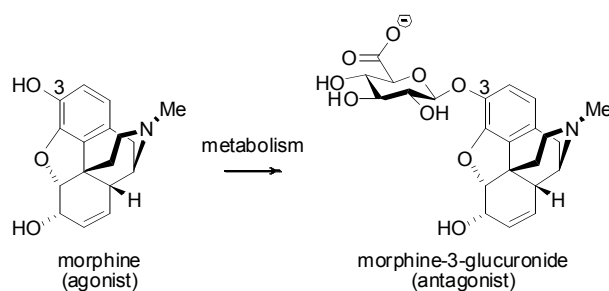


Dr Mal McLeod: Synthesis and catalysis:

Engineered enzymes for metabolite synthesis

Drug compounds are converted by the body to water soluble glucuronide (sugar-containing) metabolites to aid their excretion from the body. For example morphine is converted to morphine-3-glucuronide, a morphine receptor antagonist. Thus, glucuronide conjugates are routinely required during drug development to test for their levels and to determine the biological activity

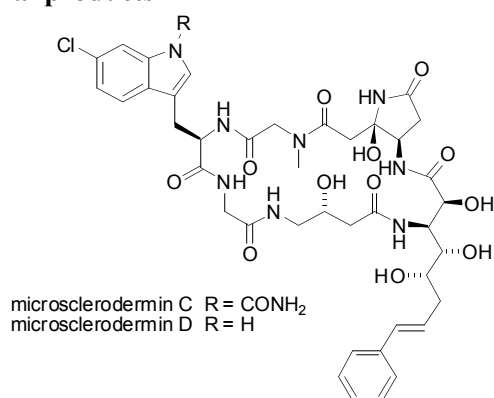


of these metabolites. Glucuronides are also extensively used in forensic science as markers of drug administration and doping in sport. This project will investigate a new class of genetically engineered enzyme to catalyse the synthesis of glucuronide conjugates under mild conditions.

Synthetic studies on the microsclerodermin natural products

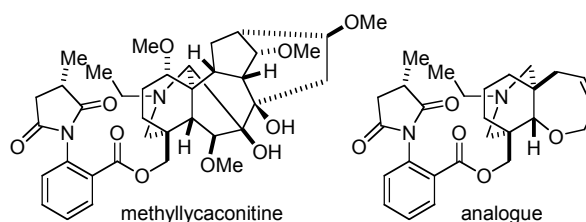
Fungal infections are currently one of the major causes of morbidity and mortality in profoundly immunocompromised individuals, including AIDS, chemotherapy and organ transplant patients. The rapid increase over the last decade of the immunocompromised patient population, coupled with increasing resistance to common anti-fungal agents has intensified the search for new fungicidal compounds. The microsclerodermins are a family of anti-fungal natural products derived from marine sponges.

The ultimate goal of this project is to discover new anti-fungal agents based on the microsclerodermins for the treatment of drug-resistant pathogenic fungal infections, and to design novel synthetic methods for the production of these compounds. The project will target the synthesis of key unusual amino acid residues needed for the total synthesis.



Medicinal chemistry of nicotinic acetylcholine receptor ligands

Nicotinic acetylcholine receptors (nAChRs) are ligand gated ion channels common in the brain and their chemistry and biology is of enormous interest in the field of medical science. Numerous receptor subtypes have been identified, so there is a pressing need for subtype selective agonists and antagonists to elucidate the biological roles of these receptors and to provide candidates for drug development.



The current project will target the $\alpha 7$ subtype which is one of the most prevalent nAChRs in the brain and has been implicated as playing a key role in conditions such as schizophrenia, Alzheimer's disease and epilepsy. We will synthesise and then test a number of new analogues of the alkaloid methyllycaconitine against nAChRs to determine which structural features give rise to potency and selectivity.

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