Dr Mal McLeod: Synthesis and Catalysis

Synthesis of natural products and analogues

The McLeod group employs organic synthesis to construct natural products and their analogues with important biological activity. Targets include the neuroactive GABAA ion channel receptor antagonist bicuculline, the dengue virus protease inhibitor panduratin A, the DNA minor groove binding pyrrolo[2,1-c][1,4]benzodiazepine anthramycin and the anti-fungal cyclic peptide microsclerodermin C. Total synthesis involves developing strategies for efficient synthesis and we often employ methodology developed within the group such as the osmium-catalysed oxyamination reaction to reach our target compounds. In many cases the products of our research are used in ongoing biological studies of the molecular target, such as the NS3/NS2B dengue virus protease or functional nicotinic acetylcholine receptors (see below).

Development of synthetic and enzyme chemistry to detect drugs in sport

Drugs are converted by the body to water soluble glucuronide or sulfate metabolites to aid their excretion from the body. For example morphine is converted to morphine 3-glucuronide, a morphine receptor antagonist. Drug conjugates are routinely required during drug development to test for their levels and to determine their biological activity. Drug conjugates are also extensively used in forensic chemistry as markers of doping in sport. We develop synthetic and enzyme chemistry for the synthesis and analysis of drug metabolites derived from designer steroids and other drugs. This involves the development and engineering of enzyme systems and the creation of new synthetic chemistry to target the unusual structures afforded. The methods are routinely employed by our collaborators at the Australian Racing Forensic Laboratory for analysis in thoroughbred, harness and greyhound racing. The methods also have application to the detection of doping in human sport.

Nicotinic acetylcholine receptor chemistry and biology

Nicotinic acetylcholine receptors (nAChRs) are ligand gated ion channels common in the brain and their chemistry and biology is of great interest in the field of medical science. We make analogues of neuroactive natural products to explore the relationship between structure and biological activity. We also work closely with collaborators at the University of Sydney on a protocol that uses cysteine mutagenesis in combination with synthetically derived reactive probes and computational models to interrogate the location and nature of ligand binding at functional nAChRs expressed in Xenopus oocytes. This approach has been used to reveal subtle conformational changes in the receptor on ligand binding, to locate hitherto unknown allosteric binding sites for neuroactive compounds, and to identify the site of action for non-competitive antagonists. The cartoon depicts a reactive analogue of the norditerpenoid alkaloid methyllycaconitine (MLA) being covalently trapped by a cysteine mutant of the α7 nAChR.

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