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Psychedelic medicines

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The recent heightened public enthusiasm for the potential therapeutic benefits of psychedelics, especially for treatment-resistant mental health conditions, has resulted in a renewed interest in the underlying science that governs their properties and pharmacology. The science of psychedelics is an intriguing, multi-disciplinary field and encompasses many known psychedelic substances, including natural, semi-synthetic and fully synthetic compounds, with several receptors, enzymes and transporters implicated in their modes of action. It is with pleasure that we present this special issue, 'Psychedelic Medicines', which provides overviews of many important aspects of the field and highlights some of the latest scientific evidence that is occupying the minds of leaders in the area.

The issue opens with a Primer Review contributed by Guest Editors, Matthew Piggott (University of Western Australia) and Peter Duggan (CSIRO), and their colleagues, Glenn Pullella (UWA) and Scott Walker (CSIRO).[1] The article provides an overview of the known chemistry and pharmacology of psychedelics, which should be particularly useful to newcomers to the field. The review covers the definition of a psychedelic substance, the different classes of psychedelics and the history of human use. It then provides more detail on the major classes of psychedelics including the ergolines, which include lysergic acid diethylamide (LSD), the tryptamines, which encompass psilocybin and *N*,*N*-dimethyltryptamine (DMT), and the phenethylamines, which include mescaline and the entactogen, 3,4-methylenedioxymethamphetamine (MDMA). The arylcyclohexylamine dissociative hallucinogens such as ketamine, and some natural products that do not fit neatly into any of the major psychedelic groupings, are also covered.

Eliza Milliken, Peter Galettis and Jenny Martin, from the Hunter Medical Research Institute and University of Newcastle, NSW,[2] present a review that focusses specifically on the mushroom-derived psilocybin, which addresses the current evidence base for psilocybin as a clinical medicine, the general chemistry and proposed mechanism of its therapeutic effect, and finishes by outlining future research directions for psilocybin-based therapies.

Jonathan Sperry and his co-authors, Daniel Anstis, Jessica Liyu and Emma Davison, from the University of Auckland,[3] present a review of the alkaloids found in *Peganum harmala*, a plant of Mediterranean, Middle Eastern and Central Asian origin. The plant has a rich history of traditional use, with consumption inducing a host of central nervous system (CNS) effects, including hallucinations. Of particular interest are the methoxy-substituted β-carbolines, monoamine oxidase inhibitors that are also important components in the traditional psychedelic Amazonian decoction ayahuasca. The review provides an overview of the 160 alkaloids so far isolated from *P. harmala*, which include several different heterocyclic alkaloid classes. Studies of the bioactivity of the identified compounds are scarce, however, and it is hoped that further biological assessment of the alkaloids detailed in the review will facilitate the identification of novel lead compounds for the treatment of psychiatric disease.

LSD is an incredibly potent psychedelic, the psychotropic activity of which was discovered by accident by Albert Hofmann in 1943 as part of a wider research program looking into a semi-synthetic lysergic acid derivatives at Sandoz Ltd. The investigation of the pharmacological properties of LSD and closely related analogues has been of fundamental importance to the development of our current understanding of the mode of action of psychedelics at a molecular level. Scott Stewart and his co-worker at the University of Western Australia, Michael Nutt, together with their industry collaborator, Nick Woolf (Woke Pharmaceuticals),[4] have produced a primer in which they discuss synthetic approaches to lysergic acid, an important precursor to LSD and its derivatives.

Recent reinvigorated interest in the therapeutic potential of psychedelics from academic and commercial sectors has placed a renewed importance on practical, scalable means of accessing this complex alkaloid scaffold, and it is expected that Stewart and co-authors' succinct contribution will be a useful resource for synthetic and process chemists working in the ergoline field.

Richard Glennon, from Virginia Commonwealth University, is a legendary medicinal chemist who, along with his co-workers, has contributed enormously to our current understanding of psychoactive agents, including drugs of abuse. Glennon and his co-author, Małgorzata Dukat,[5] have provided an interesting article that poses the question, 'quipazine: classical hallucinogen or novel psychedelic?' They point out that, although its pharmacological properties *in vitro* and in rodents suggest that quipazine could be a hallucinogen, the lack of human data precludes a definitive answer. Nevertheless, Glennon and Dukat note that the structure of quipazine is amenable to modifications that can alter its pharmacology and suggest that its analogues might be worthy of further study.

The last contribution in the psychedelic series is an original research article, contributed by one of the Guest Editors, Matthew Piggott, and five of his co-workers from the University of Western Australia.[6] MDMA used recreationally is probably exclusively racemic, but the pharmacology of its enantiomers is distinctly different. Piggott and co-workers outline the synthesis of homochiral *R*- and *S*-MDMA from chiral pool amino acids, with a key step being the nucleophilic ring-opening of homochiral *N*-tosylaziridines. The efficiency of the approach in terms of number of steps, overall yield and enantiopurity of the target amphetamines compares favourably with previously reported methods. Homochiral MDMA synthesised by Piggott and co-workers' route was investigated in non-human primate models of levodopa-induced dyskinesia in Parkinson's disease and contributed to an improved understanding of the mechanism by which racemic MDMA alleviates major side-effects of levodopa therapy.

This special issue reflects many intriguing aspects of psychedelic science, encompassing our current knowledge of traditional use, natural product and synthetic chemistry, pharmacology, neuroscience and medicine. It can be seen from all of the articles in this special issue that there is still much to be learnt, and psychedelics will continue to stimulate new scientific studies for many years to come. We acknowledge the significant efforts of all contributors who have made this timely issue possible.

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Conflicts of interest. CSIRO has undertaken research for several Australian companies whose aim is to commercialise medicinal psychedelics, including Natural MedTech, Psylo, Psychae Therapeutics and Reset Mind Sciences, and in some cases the research is ongoing. M. J. Piggott collaborates with, and is sponsored by, Emyria Ltd on MDMA-inspired medicinal chemistry research. Both authors are Guest Editors for this issue of the *Australian Journal of Chemistry* but at no stage did they have editor-level access to this or any other manuscript that they authored while it was in peer review, as is the standard practice for manuscripts submitted by an editor to this journal. The *Australian Journal of Chemistry* encourages its editors to publish in the journal and they are kept totally separate from the decision-making processes for their manuscripts. The authors have no further conflicts of interest to declare.

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Biographies

Matt Piggot completed his BSc and PhD at the University of Western Australia (UWA) under the supervision of Dieter Wege, working on the total synthesis of natural products. He then took up a post-doctoral fellowship with Martin Banwell and Chris Easton in the Research School of Chemistry at the Australian National University (ANU), involving antibiotic drug discovery in collaboration with GlaxoSmithKline. His second post-doc, with T. Ross Kelly at Boston College, was directed at the synthesis of a chemically powered, unidirectional molecular motor. Matt was appointed to an academic position at the ANU in the Department of Chemistry in 2003, and moved to the School of Molecular Sciences at UWA in 2005, where he is currently Associate Professor. Matt's research involves the design and synthesis of biologically active compounds, in the context of medicinal chemistry, chemical biology and natural product total synthesis. His endeavours in MDMA-inspired drug discovery began 20 years ago, and were recently reinvigorated through partnership with Perth-based clinical biotech company Emyria Ltd.

Peter Duggan obtained his BSc(Hons) from Flinders University and PhD from the Research School of Chemistry, Australian National University (ANU), working under the guidance of Prof. A. L. J. Beckwith. After post-doctoral work at Columbia University (New York) and the University of Cambridge, he took up academic positions, first at James Cook University, then at Monash University. In 2004, he 'stepped across the road' to CSIRO Clayton, where he is currently Senior Principal Research Scientist and Leader of CSIRO's Botanical Extracts Laboratory (BEL). Peter is also Adjunct Professor in the College of Science and Engineering at Flinders University. For more than a decade, Peter has been heavily involved in commercial research with botanical extracts. The BEL is a secure facility, in which research work with local companies is undertaken, including the analysis, processing, refinement and formulation of plant extracts, and the synthesis of phytochemicals. The laboratory has a special focus on phytocannabinoids, psychedelics and the ethical development of plant-derived medicines of importance to First Nations People.