Novel 5-MeO-DMT analogues with anxiolytic activity

Dr William Jorgensen,[a] Samuel Banister,[a] Lachlan Whish,[a] Jin Tan,[a] Grant Glatfelter,[b] Nicholas Everett[c]

[a] Xylo Bio, [b] NIDA, [c] University of Syndey

Abstract

5-MeO-DMT is a naturally occurring psychedelic under clinical investigation for the treatment of mood disorders and substance use disorders. We have synthesized a systematic library of ring-substituted analogues of 5-MeO-DMT featuring various N,N-dialkyl substitution patterns. Like 5-MeO-DMT, all analogues demonstrated potent, efficacious activation of 5-HT2A and 5-HT2C receptors. 5-MeO-DMT analogues with an additional substituent at the 4-position retained potent agonist activity at 5-HT1A, while substitutions at the 6- and 7-positions reduced or abolished 5-HT1A activity. Representative N-methyl-N-ethyl examples featuring a common ring-substituent at the 4-, 6-, and 7-positions were evaluated in the head-twitch response assay in mice, and showed dose-dependent 5-MeO-DMT-like profiles. Additionally, these analogues dose-dependently reduced immobility time in mice in an acute stress-modified tail suspension test, suggesting potential anxiolytic profile. Full details of the synthesis, receptor profiling, and behavioral evaluation of this systematic library of 5-MeO-DMT analogues will be presented.

Biography

Dr Jorgensen is Director of Medicinal Chemistry at Xylo Bio; a biotech start-up focused on the development of neuroplastogens for the treatment of psychiatric disorders. Will manages preclinical discovery and development of a diverse pipeline of small molecule serotonergic agents spanning a vast array of chemotypes. Prior to joining Xylo Bio, Will was a NHMRC Peter Doherty Biomedical Fellow based at the University of Sydney where his lab was focused on the development of brain-penetrant tubulin inhibitors for the treatment of glioblastoma, P2X4 receptor agonists and glycine receptor modulators for the treatment of chronic pain. His graduate studies were focused on the development of small molecule oxytocin receptor agonists, resulting in the formation of Kinoxis Therapeutics.