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# *Abbott Workshop Series in Synthetic Organic and Medicinal Chemistry*

## **PROFESSOR DAVID NICHOLS**

Department of Medicinal Chemistry & Molecular Pharmacology,  
Purdue University



Research encompasses medicinal and bioorganic chemistry, molecular pharmacology and toxicology. The thrust of his work focuses on the development of molecular probes to understand the role of brain monoamine neurotransmitters in normal behavior.

<http://www.mcmp.purdue.edu/faculty/?uid=drdave>

### ***Multidisciplinary Approaches to the Study of the 5-HT<sub>2A</sub> Receptor***

#### **Abstract:**

The serotonin 5-HT<sub>2A</sub> receptor is a G protein-coupled receptor (GPCR) that is thought to couple principally to G<sub>q</sub>, leading to activation of phospholipase C. Our interest in this receptor stems from its importance as a (the?) principle target for the so-called psychedelic, or hallucinogenic agents. These substances have been used throughout history to produce altered states of consciousness, and have unique psychopharmacological properties. The study of these receptors requires research efforts across several disciplines, as do most GPCRs. In the case of this receptor, however, it appears to have special importance as a critical component of sensory perception in humans, and by extension, may be a key player in mediating consciousness. Our work has centered on understanding the structure-activity relationships of agonists for the 5-HT<sub>2A</sub> receptor from a molecular perspective that has included synthesis of ligand libraries, in vitro effects on cloned wild-type and mutated receptors, in vivo studies in rats, and computational chemistry. One of our goals was to map the functional topography of the receptor, anticipating that we might gain insight into the mechanisms involved in the receptor activation process. This talk will provide a foundation for understanding the importance of 5-HT<sub>2A</sub> receptors in the brain, including background to help understand their role in mediating states of consciousness. The discussion will briefly touch upon the pharmacological concept of functional selectivity, and how it complicates the analysis of structure-activity relationships. Selected mutagenesis studies also will be presented to show how study of ligand libraries can be coupled with mutagenesis to gain insight into how agonist ligands bind to the receptor. Finally, several examples will be discussed of “rigid analogue” design, where introduction of conformational constraints has been useful to map out the active conformation of certain agonist ligands, for example LSD.

**4:15 p.m. Friday, May 11, 2012**  
**331 Smith Hall**

Host: Professor Robert Fecik

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