The remarkable complexity of the human brain is evident at all levels, from anatomical to cellular to molecular. The central molecules of synaptic signaling comprise a diverse array of integral membrane proteins that are resistant to most approaches to high resolution structural characterization. As such, chemistry provides the most powerful tool for unraveling the structures and functions of the molecules of memory, thought, and sensory perception; of Alzheimer’s, Parkinson’s, and schizophrenia. Using the mindset and methodologies of physical organic chemistry, and combining them with molecular biology, electrophysiology, and computer modelling we have probed these complex membrane proteins with a precision and subtlety normally associated with small molecule studies. We have uncovered key interactions that allow agonists to bind, and that distinguish binding of natural ligands vs. substances of abuse, including a key cation-π interaction that enables tight binding of nicotine to specific regions of the brain.