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In This Issue

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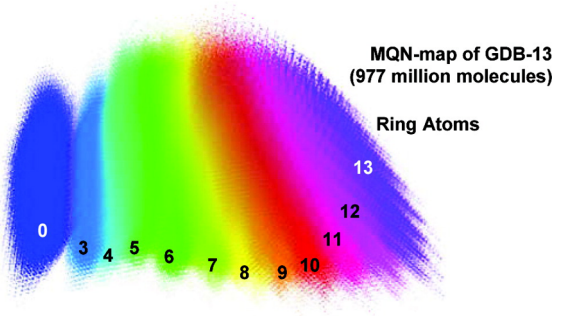
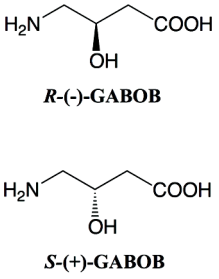
CHEMICAL SPACE EXPLORATION

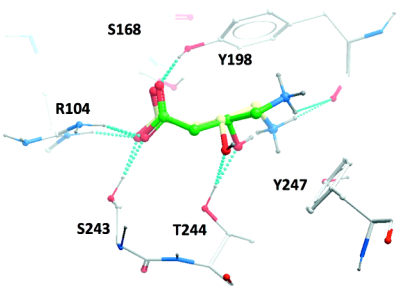


Medicinal chemists seek specific small molecule ligands that bind cellular targets to modulate cellular processes. The concept of "chemical space" is relatively new for drug development. In the current issue, Reymond and Awale (DOI: 10.1021/cn3000422) provide an overview of chemical space exploration with a focus on using a chemical universe database.

The "chemical space" encompasses a collection of all organic molecules to be considered when pursuing new drugs. The authors enumerate the chemical space and its use in the discovery of new small molecules of micromolar potency for neurotransmitter receptors such as NMDA, GLT1, and α7 nicotinic acetylcholine receptors.

A CRUCIAL RESIDUE FOR GABA$_C$ ρ_1 RECEPTOR PHARMACOLOGY

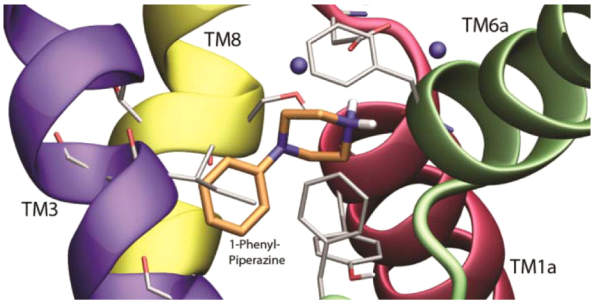




4-Amino-3-hydroxybutanoic acid (GABOB), a small molecule found in the central nervous system, activates ionotropic (GABA$_A$ and GABA$_C$) and metabotropic (GABA$_B$) receptors. The activity of GABOB is found to have anticonvulsant properties. In this issue, Yamamoto et al. (DOI: 10.1021/cn3000229) studied the effects of two enantiomers of GABOB on the GABA$_c$ ρ_1 receptor and demonstrated the importance of residue 244 in receptor function.

Homology modeling and ligand docking indicated an H-bond interaction between the hydroxyl group of GABOB and a threonine residue (T244) located on a loop in the ligand binding site of the GABA$_c$ ρ1 subunit. The authors used site-directed mutagenesis and electrophysiological studies to show that the hydroxyl group on the side chain of the amino acid at position 244 is critical for channel function.

COUNTERACTING ADDICTION



Drug abuse stimulates monoamine transporters. MDMA (commonly known "ecstasy") and 1-phenyl-piperazine (PP) analogues such as 1-(3-cholorophenyl)-piperazine inhibit normal transport in human serotonin transporters. More recently, it has been suggested that some PP analogues may actually offset addictive effects of cocaine. However, there is a gap in our understanding of the mechanism of action of these analogues. Now, Severinsen et al. (DOI: 10.1021/cn300040f) provide a clearer picture on how PP analogues bind to monoamine transporters.

The authors combined molecular dynamics simulation and docking models, organic synthesis, and molecular biology to provide insight into the interaction between PP and the central binding site of the serotonin and dopamine transporter. The details provided in this study will provide impetus for more potent PP analogues used in treatment of drug addiction.

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