ACS Chemical Neuroscience

In This Issue

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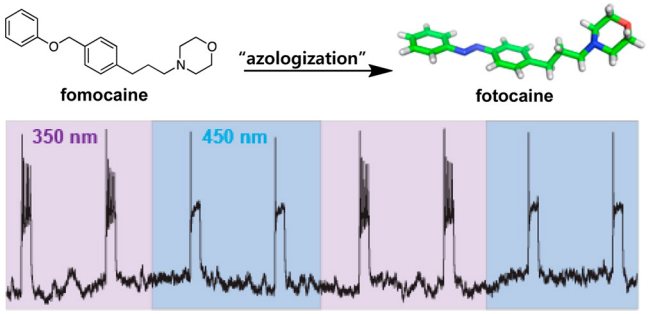
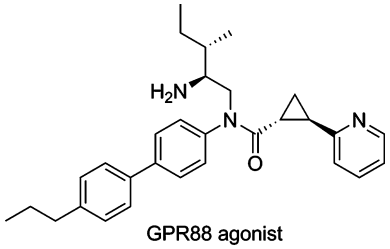
NOVEL PHOTOSWITCHABLE ION CHANNEL BLOCKER



Azologization is the strategic transformation of known drugs into photoswitchable azobenzene analogues. In the current issue, Schoenberger et al. (DOI: 10.1021/cn500070w) apply this logic to fomocaine, an important local anesthetic, and have thus developed "fotocaine", its photochromic analogue.

Fotocaine is a novel addition to the toolbox of photoswitchable ion channel blockers that have been very successful in neuroscience, pain research, and in particular in vision restoration. In contrast to existing molecules, fotocaine is not permanently charged and therefore has different pharmacodynamic properties. The authors demonstrate the ability of fotocaine to control action potential firing with light using electrophysiology on dissociated mouse hippocampal neurons and in acute mouse hippocampal brain slices.

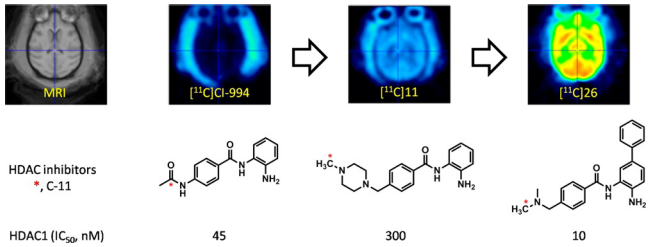
CHARACTERIZING AGONISTS OF AN ORPHAN GPCR



GPR88 is an orphan G-protein-coupled receptor that has been suggested to play an important role in the regulation of striatal functions and is a promising drug target for treating striatum-associated disorders. Now, Jin et al. (DOI: 10.1021/cn500082p) report the synthesis and pharmacological characterization of a series of agonists at GPR88 using cAMP assays.

The authors provide evidence that the signaling pathway of GPR88 is coupled through $G\alpha_i$ pathways. The assay is sufficiently robust to provide a platform for unbiased chemical screens. These novel compounds may facilitate the identification of endogenous ligands for GPR88 and the understanding of its physiological functions in vivo.

HDAC INHIBITORS FOR CNS APPLICATION



Histone deacetylase (HDAC) has emerged as an important molecular target for drug development and is also of intrinsic interest in the understanding of the contribution of epigenetic processes to gene expression. Though the majority of medical and scientific studies have focused on the role of HDAC and its inhibition in cancer, there is growing interest in developing CNS drugs as it is related to psychiatric disorders. Prior imaging studies have revealed that most of the reported HDAC inhibitors for treating CNS disorders do not penetrate the blood-brain barrier (BBB), accounting for the high doses needed to achieve therapeutic efficacy. In the current issue, Seo et al. (DOI: 10.1021/cn500021p) use MS-275 (Entinosat) as a structural template and developed a BBB permeable potent HDAC inhibitor using positron emission tomography (PET) imaging.

The authors labeled 17 benzamides with C-11, which has a half-life of 20.4 min and has the advantage of enabling multiple PET studies in the same day in the same subject. Subsequently, the authors measured brain penetration and plasma kinetics of these compounds in female baboons. These new compounds and information not only provide highly potent, brain-penetrant HDAC inhibitors for CNS applications, but also add to our knowledge of the relationship between compound structure and brain penetration.

Published: July 16, 2014

dx.doi.org/10.1021/cn500140h | *ACS Chem. Neurosci.* 2014, 5, 490−490