ACS Chemical Neuroscience

In This Issue

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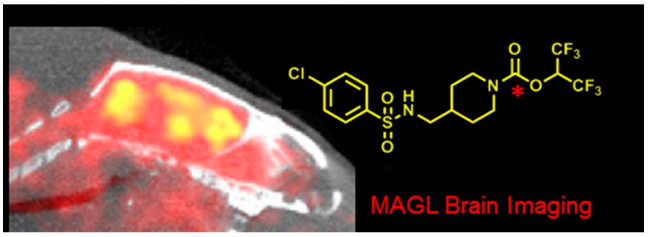
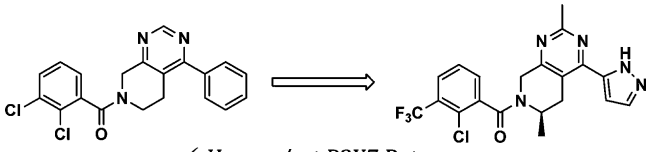
IMAGING MAGL—A PLAYER IN NEUROINFLAMMATION



Imaging tools play a vital role in determining the role of and targeting macromolecules of therapeutic importance. This is particularly true of monoacylglycerol lipase (MAGL), a serine hydrolase implicated in a range of diseases. MAGL is a leading target for novel therapies and inhibitors have been designed as tool compounds and therapeutic drugs. More specifically, MAGL is a target for treating diseases of the central nervous system, such as pain and inflammation in addition to certain psychiatric conditions. In the current issue, Wang et al. (DOI: 10.1021/acschemneuro.5b00293) provide a noninvasive imaging tool to measure the density of MAGL to accelerate drug discovery.

The authors describe the synthesis and pilot rodent imaging of a novel MAGL imaging agent, [11C]SAR127303. The imaging results demonstrated high specificity, good selectivity, and appropriate kinetics and distribution of [11C]SAR127303, validating its utility for imaging MAGL in the brain. The findings described in this paper support the translational potential for human CNS MAGL imaging for the development of MAGL inhibitors and investigation of MAGL-associated disease mechanisms.

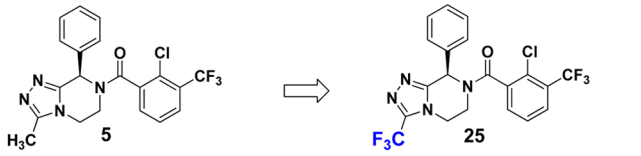
TARGETING A KEY FACTOR IN NEUROINFLAMMATION



- ✓ Human/rat P2X7 Potency
- ✓ Metabolic Stability
- ✓ IL-1β Reduction in Whole Blood
- ✓ Target Engagement
- ✓ Pharmacokinetics

Recent work has established that P2X7 receptors in the CNS play a key role in modulating neuroinflammation via IL-1β release. In the current issue, Ziff et al. (DOI: 10.1021/acschemneuro.5b00304) describe a class of brain penetrating P2X7 antagonists with high potency at both the rat and human receptors.

The authors profiled these compounds in an ex vivo radioligand binding assay and demonstrated target engagement after an oral dose. Specifically, compound **20** occupied the P2X7 receptors > 80% over a 6 h time course. In a dose–response assay, this molecule showed a plasma EC_{50} of 8 ng/mL. Overall, compound **20** shows suitable druglike properties and an oral bioavailability of 115% and 35% in rat and dog, respectively. Compound **20** was also evaluated in a whole blood assay to determine its inhibitory effects on the release of IL-1β. In this assay, compound **20** was determined to have an IC_{50} of 158 nM. This molecule and others reported in this paper will serve as additional tools to elucidate the role of P2X7 receptor in neuropsychiatric disorders related to neuroinflammation mediated by IL-1β release.



In a separate study, Chrovian et al. (DOI: 10.1021/acschemneuro.5b00303) describe optimization efforts of novel, druglike P2X7 antagonists and, importantly, how key structural functionality was incorporated into the molecules that allowed them to distribute effectively into the brain. This work culminates with the identification of a potent antagonist that demonstrates excellent receptor occupancy as measured by ex vivo ligand binding autoradiography experiments in the rat. In vitro and in vivo DMPK properties and selectivity data of the key compound are reported, as well as in vitro DMPK for four compounds leading to the discovery of the lead. The work discusses the SAR including synthesis and characterization of 21 novel phenyl substituted triazolopyrazines.

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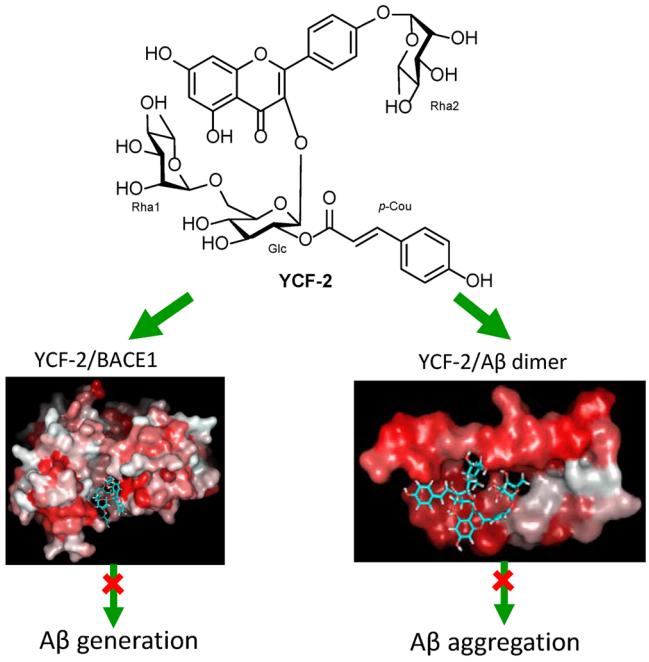
LEAD COMPOUND FOR TREATING ALZHEIMER'S DISEASE



The currently available one-target strategies may be insufficient to impede the pathological processes of Alzheimer's disease (AD). Instead, the screening of multifunctional agents that can hit multiple targets simultaneously may be a reasonable strategy for the treatment of AD. In the current issue, Yang et al. (DOI: 10.1021/acschemneuro.6b00091) report a novel multifunctional compound for potentially treating AD.

The compound Camellikaempferoside B (YCF-2) from Fuzhuan brick tea exhibited multiple properties by decreasing Aβ production, moderating Aβ oligomer structure, and mitigating Aβ-mediated cytotoxicity and neuroinflammation. This chemical offers novel lead structure for the treatment of AD.

DOI: 10.1021/acschemneuro.6b00100
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