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In This Issue

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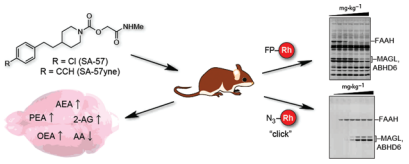
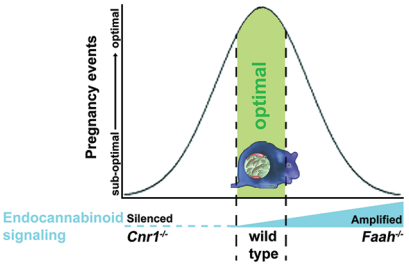
POTENT NEW DUAL INHIBITOR



The endocannabinoid signaling system (EC) is associated with a number of physiological functions such as mood, appetite, inflammation, pain sensation, reproduction, and neurodegenerative disorders. As a result, receptors and enzymes that comprise the EC have emerged as important therapeutic targets. Specifically, fatty acid amide hydrolase (FAAH), that degrades the endocannabinoid transmitter anandamide (AEA), and monoacylglycerol lipase (MAGL), that degrades the endocannabinoid transmitter, 2-arachidonoylglycerol (2-AG), are important drug targets. In this issue, Niphakis et al. (DOI: 10.1021/cn200089j) report a potent new compound with inhibitory effects on both FAAH and MAGL.

The authors tested a series of *O*-hydroxyacetamide carbamate inhibitors against FAAH and MAGL and discovered a new compound, SA-57, with potent activity at low doses against FAAH and two 2-AG hydrolases, MAGL and ABHD6, in vivo. SA-57 provides an important breakthrough in the selective inhibition of EC targets without deleterious side effects.

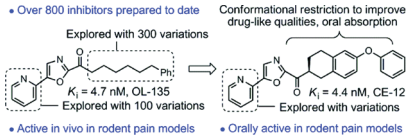
THE RELATIONSHIP BETWEEN ENDOCANNABINOIDS AND FEMALE FERTILITY



Marijuana is a drug frequently used for recreational purposes. The identification of the psychoactive ingredient in marijuana, Δ9-tetrahydrocannabinol, led to the discovery of other cannabinoid-like compounds, which were together named endocannabinoids. The endocannabinoid system (EC) has been implicated in several physiological functions including female fertility. In this issue, Sun and Dey (DOI: 10.1021/cn300014e) review recent work on the adverse effects of improper endocannabinoid signaling on female reproduction.

Studies in several mouse models show that a normal pregnancy requires precise functioning of the EC in the blastocyst and uterus. Imbalanced signaling adversely affects preimplantation, embryo development, oviductal embryo transport, implantation, placentation, and parturition. Current evidence points to the EC playing a regulatory role in reproduction, since deletions of EC genes result in subfertile mice.

INHIBITING TARGET ENZYME IMPLICATED IN PAIN AND SLEEP DISORDERS



Fatty acid amide hydrolase (FAAH) is a member of the serine hydrolase family and is distributed in the central nervous system. FAAH degrades fatty acid amide signaling molecules such as anandamide and oleamide. Recent studies have shown that FAAH may be a therapeutic target for treating a wide range of ailments including pain, inflammation, and sleep disorders. In the current issue, Otrubova and Boger (DOI: 10.1021/cn2001206) provide a comprehensive overview on the development of an important class of FAAH inhibitors.

The authors describe the discovery and development of highly potent and selective α-ketoheterocycle inhibitors of FAAH. These inhibitors have been used to determine the mechanism by which fatty acid amide hydrolysis is achieved and to corroborate the role of FAAH in pain and sleep disorders.

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