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IN THIS ISSUE

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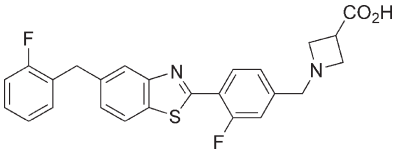
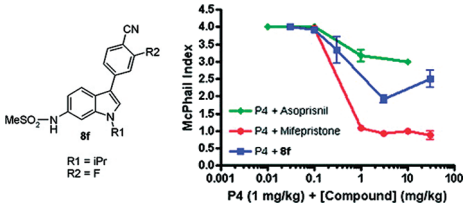
Agonists of the Sphingosine-1-Phosphate Type 1 Receptor

Sphingosine-1-phosphate modulates diverse cellular processes including migration, adhesion, proliferation, and differentiation in part by interacting with G protein-coupled receptors widely expressed in the immune, cardiovascular, and central nervous systems. One such receptor, S1P1, is found in abundance in lymphocytes. Potent agonists of this receptor are described in research in the journal. Lanman et al. (DOI: 10.1021/ml100228m) describe the optimization of a benzofuran-based S1P1 receptor agonist that did not display proconvulsive activity, demonstrating potential for clinical development. Saha et al. (DOI: 10.1021/ml100227q) describe another class of benofuran derivatives that were optimized for potency at the S1P1 receptor and limited cross-reactivity at the S1P3 receptor. These compounds were optimized for efficacy in preclinical animal models of multiple sclerosis. Cee et al. (DOI: 10.1021/ml100306h) optimized a class of thiazolopyridine S1P1/S1P5 dual agonists that when administered orally in an animal model were shown to reduce the severity of autoimmune encephalomyelitis. The S1P1 agonists described in these three studies demonstrate suitable pharmacological properties and are excellent starting points for new therapeutic development.



Noninvasive Treatment of Uterine Fibroids

Uterine fibroids are benign tumors that can cause abnormal menstrual bleeding, pelvic pain, and decreased fertility. Treatment options include hysterectomy, which is expensive, invasive, and unacceptable for women seeking to become pregnant in the future. Treatment options that are noninvasive would therefore alleviate many of these concerns. However, currently, pharmaceutical treatments for uterine fibroids primarily reduce size prior to surgical excision. Progesterone is a hormone that regulates the female reproductive cycle. The receptor for this hormone is a member of the nuclear receptor family of ligand-dependent transcription factors. The receptor can be regulated by natural and synthetic compounds ranging from full agonists to full antagonists. Here, Richardson et al. (DOI: 10.1021/ml100220b) describe a class of novel 3-aryl indole receptor agonists that could serve as compounds useful in the development of noninvasive therapeutics for uterine fibroids.



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