Development of a novel peroxisome proliferator-activated receptor alpha activator to treat nonalcoholic steatohepatitis

Keisuke Tachibana, Takefumi Doi

Grad. Sch. Pharm. Sci., Osaka Univ.

Nonalcoholic steatohepatitis (NASH), which is characterized by triglyceride accumulation in hepatocytes, causes liver fibrosis and cancer. Peroxisome proliferator-activated receptor alpha (PPARα), a ligand-activated transcription factor, is predominantly expressed in the liver, where it activates fatty acid catabolism and reduces plasma triglyceride levels. Recent studies suggest that PPARα is a good therapeutic target for NASH. In this study, to detect PPARα activators, we established reporter cell lines to quantify the effects of ligands on PPARα activity using a tightly tetracycline-regulated human hepatoblastoma cell line that can be induced to express full-length human PPARα. By screening a chemical library using this cell line, we successfully identified 1*H*-pyrazolo-[3,4-*b*]pyridine-4-carboxylic acid derivatives as hit compounds with different basic skeletons from those of known PPARα agonists. This compound upregulated PPARα transcriptional activity in a dose-dependent manner, and induced PPARα target genes both in vitro and in vivo. Treatment of NASH model mice with this compound via oral gavage for 6 weeks led to a reduction in the plasma triglyceride level and a slight decrease in the liver hydroxyproline content. We are currently conducting X-ray crystallographic studies of the PPARα ligand-binding domain and complexes of these compounds to design and develop more effective drugs. Although further investigations are needed, this novel PPARα ligand might be a candidate drug for treating NASH.