27O-ISMS41 Development of Novel Non-fibrate PPARα Activator for Metabolic Diseases

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Peroxisome proliferator-activated receptor alpha (PPARα) is a ligand-activated transcription factor that belongs to the nuclear hormone receptor superfamily. PPARα is mainly expressed in the liver, where it activates fatty acid oxidation and lipoprotein metabolism, and improves plasma lipid profiles. Thus, PPARα activators are used to treat dyslipidemia.

In this study, to detect PPARα activators, we established reporter cell lines to quantify the effect 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 an established PPARα-activator screening system, we successfully identified hit compounds with different basic skeletons from that of known PPARα agonists. These non-fibrate compounds up-regulated PPARα transcriptional activities in a dose-dependent manner, and the half-maximal effective concentrations of these compounds were lower than that of fenofibrate. Finally, when high fructose-supplemented rats with elevated plasma triglyceride levels, were treated with fenofibrate or a non-fibrate compound for 14 days, the non-fibrate compound was more effective than fenofibrate in reducing plasma triglyceride levels. The above results suggest that these non-fibrate compounds might be effective drugs for the treatment of metabolic diseases.