

Highly selective PPAR δ modulators help ascertain role of PPAR α in the mouse model of muscle regeneration

American Chemical Society Fall Meeting, August 23, 2021, MEDI Oral Presentations II, PAPER ID: 3580980

Early generation PPAR δ modulators, including GW501516, were found to be efficacious in a mouse model of muscle regeneration (thermal injury model). In the literature, the efficacy was attributed to the activity for PPAR δ receptor and their selectivity over PPAR α and PPAR γ receptors. With the series of highly PPAR δ -selective (>100,000 fold over other PPARs) compounds, we observed that the efficacy was reduced in the model of muscle regeneration as the compounds became more and more selective for PPAR δ receptor. A careful study of PPAR δ modulators with varying degrees of selectivity over PPAR α receptor, revealed that the muscle regeneration activity correlated better with the PPAR α activity (and not PPAR δ as was previously proposed). We then used a known selective PPAR α modulator to confirm the findings. This study highlights the power of medicinal chemistry tools in understanding contributions of receptor subtypes in animal models.