Anthranilic acid derivatives as nuclear receptor modulators–development of novel PPAR selective and dual PPAR/FXR ligands

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Nuclear receptors, especially the peroxisome proliferator activated receptors (PPARs) and the farnesoid X receptor (FXR) fulfill crucial roles in metabolic balance. Their activation offers valuable therapeutic potential which has high clinical relevance with the fibrates and glitazones as PPAR agonistic drugs. With growing knowledge about the various functions of nuclear receptors in many disorders, new selective or dual ligands of these pharmaceutical targets are however still required. Here we report the class of anthranilic acid derivatives as novel selective PPAR or dual FXR/PPAR ligands. We identified distinct molecular determinants that govern selectivity for each PPAR subtype or FXR as well as the amplitude of activation of the respective receptors. We thereby discovered several lead compounds for further optimization and developed a highly potent dual PPARα/FXR partial agonist that might have a beneficial synergistic effect on lipid homeostasis by simultaneous activation of two nuclear receptors involved in lipid metabolism.
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