Polyacetylenes from Notopterygium incisum–New Selective Partial Agonists of Peroxisome Proliferator-Activated Receptor-Gamma

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Résumé en anglais	Peroxisome proliferator-activated receptor gamma (PPARγ) is a key regulator of glucose and lipid metabolism and therefore an important pharmacological target to combat metabolic diseases. Since the currently used full PPARγ agonists display serious side effects, identification of novel ligands, particularly partial agonists, is highly relevant. Searching for new active compounds, we investigated extracts of the underground parts of *Notopterygium incisum*, a medicinal plant used in traditional Chinese medicine, and observed significant PPARγ activation using a PPARγ-driven luciferase reporter model. Activity-guided fractionation of the dichloromethane extract led to the isolation of six polyacetylenes, which displayed properties of selective partial PPARγ agonists in the luciferase reporter model. Since PPARγ activation by this class of compounds has so far not been reported, we have chosen the prototypical polyacetylene falcarindiol for further investigation. The effect of falcarindiol (10 µM) in the luciferase reporter model was blocked upon co-treatment with the PPARγ antagonist T0070907 (1 µM). Falcarindiol bound to the purified human PPARγ receptor with a *Ki* of 3.07 µM. *In silico* docking studies suggested a binding mode within the ligand binding site, where hydrogen bonds to Cys285 and Glu295 are predicted to be formed in addition to extensive hydrophobic interactions. Furthermore, falcarindiol further induced 3T3-L1 preadipocyte differentiation and enhanced the insulin-induced glucose uptake in differentiated 3T3-L1 adipocytes confirming effectiveness in cell models with endogenous PPARγ expression. In conclusion, we identified falcarindiol-type polyacetylenes as a novel class of natural partial PPARγ agonists, having potential to be further explored as pharmaceutical leads or dietary supplements.
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