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Pirinixic Acid Derivatives as Potent Dual Agonists of the Peroxisome Proliferatior Activated Receptor Alpha and Gamma

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Peroxisome proliferator-activated receptors (PPARs) comprise a three-member subgroup ($\alpha, \gamma, \beta/\delta$) within the nuclear hormone receptor family of ligand-activated transcription factors that have been the focus of extensive research during the past decade. Being activated by the fibrate and glitazone types of drugs, PPARα and PPARγ are among the major targets for the treatment of dyslipidemia and type 2 diabetes. Dual PPARα, γ agonists are currently under investigation for the combined treatment of both diseases, which, furthermore, are frequently associated. In addition, PPAR is gaining more and more evidence to be an anti-inflammatory target.

Pirinix acid (WY-14643), which is a common research tool for PPARα, was developed in the 1970s as an antihypercholesterolemic agent and was found to be a peroxisome proliferator, whereas the target of pirinix acid, the peroxisome proliferator activated receptor, was discovered in 1990, which led to the discovery of the PPARα and the less known PPARγ agonism of pirinix acid.

Starting with pirinix acid which is a moderately active dual PPARα, γ agonist we improved potency at the human PPARα and PPARγ by substituting the α-position with an aliphatic chain. The maximal effect was achieved at a chain length of four and six carbon atoms respectively, leading to an activity induction by factor 36 at PPARα and 18 at PPARγ respectively.

Our lead structure optimisation programm also revealed that the mere substitution of the dimethyl aniline moiety of pirinix acid by quinoline leads to a total loss of PPARα, γ agonism, whereas concomitant α-substitution with n-butyl or n-hexyl groups restores and even enforces PPAR activation, leading to potent dual PPARα, γ agonists. Molecular docking of those compounds suggests a binding mode resembling to that of tesaglitazar.

References

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