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Design synthesis and biological evaluation of fibrate analogues as PPAR agonists

Peroxisome Proliferator-Activated Receptors (PPARs) are nuclear hormone receptors expressed in metabolically active tissues. To date, three isoforms namely PPARα, PPARγ and PPARδ are identified; they are important in lipid metabolism and glucose homeostasis. Dual PPARα/γ agonists are able to reduce side effects of selective PPARα or PPARγ agonists and may be used in dyslipidemia and type 2 diabetes mellitus simultaneously. Furthermore, PPARα/γ/δ pan-agonists could alter carbohydrate and lipid metabolism in a coordinated manner. In the last years, PPARs are emerging as promising pharmacological targets also for the treatment of neurodegenerative diseases. Fibrate analogues active as PPAR agonists have, as typical pharmacophore, a carboxylic acid head and an aromatic ring with or without various spacers. In the past, we reported different fibrate analogues with good activation of PPARs. One of the best compounds was a selective PPARγ agonist GL516 (EC_{50}=0.8 μM). This molecule was a potential neuroprotective agent because proved effective in restoring catalase activity reducing reactive oxygen species (ROS) production and decreasing the apoptosis. Another promising molecule was a dual PPARα/γ agonist GL479 (αEC_{50}=0.6μM and γEC_{50}=1.4μM). This compound was crystallized with the PPARα and PPARγ to understand that it occupies the ligand-binding pocket of PPARα and PPARγ in two distinct conformations. In view of these promising results, and in order to gain more insight on the structure-activity relationships, we synthesized new GL479 analogues with different substituents in para to the phenyldiazenyl moiety and with the oxygen of the linker in para to the 2-methyl-2-phenoxypropanoic group. Moreover, to investigate how the azo linker modification influences the activity we synthesized nitro, amino, ureidic, amide and sulfonamide derivatives. All compounds were tested on PPARs and the results showed that some of these are promising candidates to develop new more potent PPAR agonists potentially active as neuroprotective agents.

Figure: General structure of fibrate analogues and its modifications

Recent Publications

1. Den Broeder MJ, Kopylova VA, Kamminga LM and Legler L (2015). Zebrafish as a model to study the role of peroxisome proliferating-activated receptors in adipogenesis and obesity. PPAR Res. 358029.
2. Bordet R, Ouk T, Petrault O, Gele P, Gautier S, Laprais M, Deplanque D, Duriez P, Staels B, Fruchart JC and Bastide M (2006) PPAR: a new pharmacological target for neuroprotection in stroke and neurodegenerative diseases. Biochem. Soc. Trans., 34: 1341-1346.
3. Giampietro L, D'Angelo L, Giancristofaro A, Ammazzalorso A, De Filippis B, Fantacuzzi M, Linciano P, Maccallini C and Amoroso R (2012) Synthesis and structure–activity relationships of fibrate-based analogues inside PPARs. Bioorg. Med. Chem. Lett. 22:7662-7666.

4. dos Santos JC, Bernardes A, Giampietro L, Ammazzalorso A, De Filippis B, Amoroso R, Polikarpov I (2015) Different binding and recognition modes of GL479, a dual agonist of Peroxisome Proliferator-Activated Receptor α/γ. J. Struct. Biol. 191:332–340.

Biography

Letizia Giampietro has completed bachelor's degree in Pharmacy and received her PhD in Medicinal Chemistry from the University "G. D'Annunzio of Chieti" of Chieti (Italy). From 2006, she is working as an Assistant Professor of Pharmaceutical Analysis. She has published more than 40 papers in reputed journals. Her research interests include Medicinal Chemistry and are above all focused towards the synthesis of fibrate derivatives active on Peroxisome Proliferator-Activate Receptors (PPARs). Lately, her research is directed to the synthesis of small molecules with anticancer, neuroprotective and antioxidant activity.

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