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Novel PPARα Antagonists Bearing Stilbene or Bioisosteres Endowed with Antiproliferative Effects in Cancer Cell Lines

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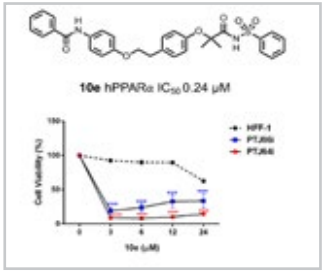
Biography

Alessandra Ammazzalorso obtained her PhD in Pharmaceutical Sciences from the University of Chieti, Italy, in 2001. Since 2004 she has been an Assistant Professor of Medicinal Chemistry at the University of Chieti, Department of Pharmacy. Her research interests include the design and synthesis of small-molecule drugs, mainly compounds targeting Peroxisome Proliferator-Activated Receptors, aromatase and nitric oxide synthase

Peroxisome Proliferator-Activated Receptors (PPARs) have been widely studied in the last decades, and they attracted the attention of scientists as promising therapeutic targets. Intensive efforts by researchers produced a wide panel of drugs targeting the three PPAR subtypes (PPARα, PPARβ, PPARγ) able to modulate important metabolic functions. PPAR activation is involved in several physiologic pathways, as lipid and glucose metabolism, insulin sensitivity, energy homeostasis, and cell differentiation. Fibrates and thiazolidinediones, respectively synthetic PPARα and PPARγ agonists, are currently used for the treatment of hyperlipidemia and hyperglycemia, in patients affected by type 2 diabetes and metabolic syndrome[1].



In recent years, an increased expression of PPARα has been found in different tumors: it is well known that cancer cells present altered metabolic pathways, switching from the glycolysis to fatty acid oxidation metabolism. In this scenario, PPARα antagonists emerged as novel potential drugs in tumors overexpressing PPARα, by interfering with cellular survival and metastasis formation.[2] In vitro anticancer effects were found for PPARα antagonists in chronic lymphocytic leukemia [3], renal cancer, colorectal and pancreatic cancer [4], paraganglioma [5].

In this study we report on the synthesis of novel PPARα antagonists bearing stilbene or its bioisosteres, starting from the structure of a dual PPARα/γ agonist, previously synthesized in our laboratory. We explored the cytotoxicity of the novel compounds in different cancer cell lines (colorectal, pancreatic, renal, paraganglioma) expressing PPARα.

Publications

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