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Research paper

Synthesis, *in vitro* evaluation, and molecular modeling investigation of benzenesulfonimide peroxisome proliferator-activated receptors α antagonists

Alessandra Ammazzalorso [a, *], Antonio Carrieri [b], Fabio Verginelli [c, d], Isabella Bruno [a], Giuseppe Carbonara [b], Alessandra D'Angelo [a], Barbara De Filippis [a], Marialuigia Fantacuzzi [a], Rosalba Florio [c, d], Giuseppe Fracchiolla [b], Letizia Giampietro [a], Antonella Giancristofaro [a], Cristina Maccallini [a], Alessandro Cama [c, d], Rosa Amoroso [a, **]

[a] Unità di Chimica Farmaceutica, Dipartimento di Farmacia, Università"G. d'Annunzio", Chieti, Italy
[b] Dipartimento di Farmacia-Scienze del Farmaco, Università di Bari, Italy
[c] Unità di Patologia Generale, Dipartimento di Farmacia, Università "G. d'Annunzio", Chieti, Italy
[d] Aging Research Center (Ce.S.I.), Università "G. d'Annunzio", Chieti, Italy

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ABSTRACT

Recent evidences suggest a moderate activation of Peroxisome Proliferator-Activated Receptors (PPARs) could be favorable in metabolic diseases, reducing side effects given from full agonists. PPAR partial agonists and antagonists represent, to date, interesting tools to better elucidate biological processes modulated by these receptors. In this work are reported new benzenesulfonimide compounds able to block PPARα, synthesized and tested by transactivation assays and gene expression analysis. Some of these compounds showed a dose-dependent antagonistic behavior on PPARα, submicromolar potency, different profiles of selectivity *versus* PPARγ, and a repressive effect on CPT1A expression. Dockings and molecular dynamics on properly selected benzenesulfonimide derivatives furnished fresh insights into the molecular determinant most likely responsible for PPARα antagonism.

1. Introduction

Peroxisome Proliferator-Activated Receptors (PPARs) belong to the nuclear receptor family, which includes receptors for steroids, retinoids, thyroid hormones and vitamin D. PPARs are transcription factors, able to control the expression of genes involved in many important cellular functions, such as regulation of glucose and lipid metabolism, sensitivity to insulin and energetic homeostasis [1,2]. The three PPAR subtypes, PPARα, PPARγ and PPARδ, show a different tissue distribution, and they represent interesting target for the treatment of cardiovascular diseases, such as dislipidemia, type II diabetes and metabolic syndrome [3–5].

Potent and selective agonists for three PPAR subtypes have been developed, but more recent strategies aimed to molecules able to activate more than one isotype, with a balanced potency at each receptor. Dual agonists, pan-agonists and selective PPAR modulators (SPPARMs) represent the results of intense research efforts, with the aim to afford new compounds efficacious in metabolic disorders, and with a safer toxicological profile [6–9].

Unfortunately some major problems on safety arose for many of these compounds: PPARα/γ dual agonists, such as muraglitazar and tesaglitazar, were discontinued during clinical trials because of increased cardiovascular risks [10]. A moderate activation of PPARs has been emerging as a new therapeutic option: research on partial agonists, inverse agonists and antagonists of PPARs is gaining

* Corresponding author. Dipartimento di Farmacia, Università di Chieti, via dei Vestini 31, 66100 Chieti, Italy.
** Corresponding author. Dipartimento di Farmacia, Università di Chieti, via dei Vestini 31, 66100 Chieti, Italy.
E-mail addresses: aammazzalorso@unich.it (A. Ammazzalorso), ramoroso@unich.it (R. Amoroso).

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interest in the scientific community, promising beneficial effects in controlling glucose and lipid metabolism [11–14].

An increasing body of data suggests PPAR antagonists could represent new therapeutic tools for treating a number of diseases, including metabolic, cardiovascular, inflammatory pathologies, and cancer [15]. Many of these compounds have been designed based on the Hashimoto's hypothesis, that identifies the helix 12 (H12) misfolding as a crucial event to determine the repression of PPARs [16].

In Fig. 1 is depicted a selection of antagonists of three PPAR subtypes. A moderate activation of PPARγ has been related to beneficial effects on insulin resistance and obesity: SR202 enhances insulin sensitivity in diabetic mice, with an additional positive effect on lipid profile [17]. T0070907 is able to block adipocyte differentiation and displays antitumoral effects in hepatocellular, esophageal, and squamous cell carcinoma [18]. Also CDDO-Me induces anticancer effects by antagonizing PPARγ, inhibiting the growth and proliferation in a wide variety of tumor cell lines [19]. PPARδ antagonists showed promising effects on cell proliferation in different cancer cell lines: SR13904 displayed inhibitory effects on cellular proliferation and survival in lung, prostate, breast and liver tumor cell lines [20]. Many studies have been focused on these compounds, in the attempt to clarify structure-activity relationships and improve their pharmacokinetic profile [21–24].

Otherwise, the knowledge about PPARα antagonists is to date quite limited. A small number of antagonists have been described, and their biological potential appears not completely clear. Recently, interesting data have been presented for PPARα antagonists GW6471 [25] and MK886 [26]; some scientific evidences suggest a possible involvement in the growth and the survival of cancerous cells. More in detail, GW6471 showed a marked effect in glioblastoma models, being able to reduce lipid droplets, related to the tumor malignancy grade [27]; in addition, it was tested in renal cell carcinoma cell lines (RCC), showing a clear arrest of cell growth in G0/G1 phase and the induction of apoptosis [28]. MK886 was effective in causing killing of cells in a model of chronic lymphocytic leukemia (CLL), determining also the immunogenic death of proliferating cells [29]. These evidences suggest PPARα inhibition could represent a novel therapeutic approach for different tumoral pathologies.

In the search for new PPARα antagonists, we previously synthesized benzenesulfonimide compounds, derived from carboxylic acids [30], found PPARα antagonists at micromolar concentration (Fig. 2) [31]. These compounds were recently obtained *via* a titanium-mediated synthetic approach, by using esters as acylating agent [32]. They were able to antagonize the transcriptional response induced by PPARα agonist GW7647 in a dose-dependent fashion. A repressive effect on carnitine palmitoyltransferase 1 (CPT1A), a key enzyme involved in fatty acid β-oxidation, was also demonstrated.

The bioisosteric replacement of carboxylic moiety has been proven to be favorable for keeping affinity with PPARα ligand

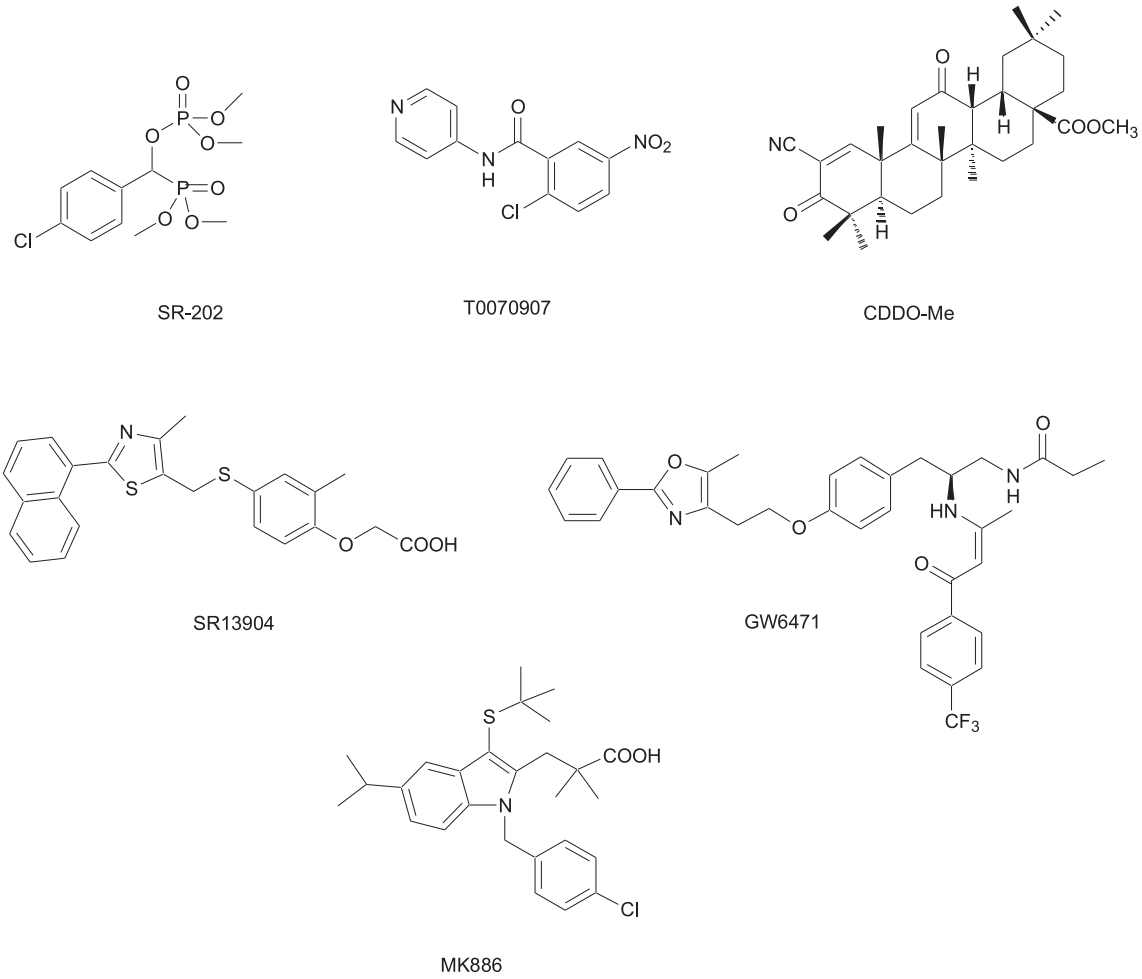

Fig. 1. Selected antagonists of three PPAR isoforms: SR-202, T0070907, CDDO-Me (PPARγ antagonists), SR13904 (PPARδ antagonist), GW6471 and MK886 (PPARα antagonists).