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Original article

# A short series of antidiabetic sulfonylureas exhibit multiple ligand PPARγ-binding patterns

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#### Abstract

The present work explores the PPAR $\gamma$ -activating properties of a series of eight sulfonylureas, using transfection experiments with 293T cells, and rosiglitazone as a reference PPAR $\gamma$  agonist. In the same time, results from these *in vitro* experiments are compared to those generated by a sound *in silico* PPAR $\gamma$ -ligand docking procedure combined to a simple and astute strategy analysis. The latter consists of building up a dendrogram (decision tree-like diagram) by applying three successive criteria, namely stability, conformational shape and H-binding strength of the docked sulfonylurea or rosiglitazone. This original dendrogram approach avers to be a successful way to account for our biochemical data. It discriminates also various PPAR $\gamma$ -binding patterns from our small series of compounds. The recognition of these patterns is extremely important because of the extraordinary potentialities of PPAR $\gamma$  ligands as therapeutic agents in diabetes, cancer, cardiovascular and neurological disorders.

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Keywords: Sulfonylureas; Rosiglitazone; PPARy; Ligand binding domain; Molecular interactions; In silico studies; Docking; 2PRG structure; Selective PPAR modulation (SPPARM)

## 1. Introduction

Antidiabetic sulfonylureas (compounds 1-8 in Fig. 1) exhibit structural analogies with thiazolidinedione compounds

pecially, the respective chemical platforms to which substitutions are added for declination of drug family members are characterized by a phenyl group separated by two atoms from a succession of a carbonyl group and a nitrogen atom. Substitutions occur on this nitrogen on one side of the molecule and in the para position of the phenyl group for the other side in the two drug families (see chemical platforms and substitutions depicted in Fig. 1). Based on these structural analogies, experiments were carried out to compare PPAR $\gamma$ -activating properties of oral antidiabetic sulfonylureas to those of rosiglitazone. Our work actually comes in the wake of the recent

of the glitazone series such as rosiglitazone (Fig. 1). More es-

Abbreviations: PPAR, peroxisome proliferator-activated receptor; SPPARM, selective PPAR modulation; LBD, ligand binding domain; FMOC, N-[9-fluorenylmethoxycarbonyl]; GOLD, Genetic Optimisation for Ligand Docking; PDB, Protein Data Bank, 2PRG is a PDB reference for a structure of PPAR $\gamma$  crystallised with rosiglitazone; DMSO, dimethyl sulfoxide.

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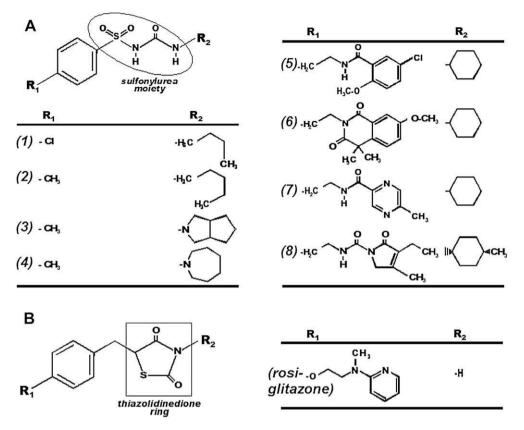


Fig. 1. Oral antidiabetic sulfonylureas (A) and glitazone (B) chemical structures. (A) Oral antidiabetic sulfonylureas of the first generation are represented by chlorpropamide (1), tolbutamide (2), gliclazide (3), tolazamide (4), those of the second generation include glibenclamide (5) and glipizide (7) and the more recent members are gliquidone (6) and glimepiride (8). (B) The reference thiazolidinedione compound used in the present study is rosiglitazone.

report by Fukuen et al. [1] who, in a concern to study extrapancreatic effects of antidiabetic sulfonylureas, have documented their PPAR $\gamma$ -activating properties. Our concern is, however, different from these authors. In addition to some structural analogies between rosiglitazone and sulfonylureas, we are currently exploring the neuroprotective potential of PPAR $\gamma$  and thus novel ligands of this nuclear receptor, having recently collected data showing that FMOC-L-leucine, a PPARy agonist [2], can protect both mature and immature brains [3]. While with a slightly different series of compounds we confirm the data of Fukuen et al. [1] that more recent versus old generation sulfonylureas activate PPAR $\gamma$ , we also present here noteworthy in silico data showing that although each sulfonylurea is characterized by a given type of interaction mode towards PPAR $\gamma$ , this group of the eight sulfonylureas tested was capable of generating five classes or modes of PPARy-binding profiles, making this short series of compounds valuable for exploring interactive potentialities of the PPAR $\gamma$ -binding pocket.

## 2. Materials and methods

#### 2.1. In vitro experiments

Oral antidiabetic sulfonylureas were purchased from Sigma Co (St. Louis, MO) or purified from the respective commercial preparation. Rosiglitazone was a gift from Dr R. Heyman (X-ceptor Therapeutics).

Stimulation of PPAR $\gamma$  transactivaton by antidiabetic sulfonylureas and rosiglitazone was studied on 293T cells cultured in DMEM + 10% FBS. Cells were cotransfected by CaCl<sub>2</sub> precipitation with a plasmid containing three synthetic PPAR response elements (J3TK-Luc) (pGL3-(Jwt)3TKluc), and either an empty plasmid or an expression vector encoding human PPAR $\gamma$  (pSG5, pSG5-PPAR $\gamma$ ) and pCMV- $\beta$ gal to control for transfection efficiency [2]. Four hours later, the cells were washed with fresh medium and treated with either rosiglitazone (rosiglitazone, 10<sup>-7</sup> M), the antidiabetic sulfonylureas (10<sup>-5</sup> M) or DMSO (vehicle).

Activating sulfonylureas were also tested at various concentrations ranging from  $10^{-9}$  to  $10^{-5}$  M for dose-dependent effects or at  $10^{-5}$  M combined or not with  $10^{-8}$  M rosiglitazone for studying additive effects of sulfonylureas and the glitazone. Luciferase activity was measured 24 h later in cell extracts.

#### 2.2. In silico experiments

#### 2.2.1. Docking algorithm

In silico binding to PPAR $\gamma$  of sulfonylureas was studied using the protein-ligand docking program GOLD (Genetic Optimisation for Ligand Docking) [4]. This program explores in detail the conformational range of the ligand with genetic Download English Version:

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