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## A short series of antidiabetic sulfonylureas exhibit multiple ligand PPAR $\gamma$ -binding patterns

Alban Arrault <sup>a</sup>, Stéphane Rocchi <sup>b</sup>, Frédéric Picard <sup>c</sup>, Pierre Maurois <sup>d</sup>,  
Bernard Pirotte <sup>e</sup>, Joseph Vamecq <sup>f,\*</sup>

<sup>a</sup> Chemoinformatics Group, Institut de Chimie Organique et Analytique, UMR CNRS 6005, Université d'Orléans, BP 6759, F-45067 Orléans Cedex 2, France

<sup>b</sup> Inserm U597, Faculté de Médecine, 28 Avenue de Valombrose, F-06107 Nice Cedex 2, France

<sup>c</sup> Centre de recherche de l'Hôpital Laval local Y3106, 2725 chemin Sainte-Foy, Québec City, Québec, Canada G1V 4G5

<sup>d</sup> CNRS UMR 8162, Centre Chirurgical Marie Lannelongue, F-92350 Le Plessis-Robinson, and Faculté de Pharmacie, Université Paris-Sud 11, F-92296 Châtenay-Malabry, France

<sup>e</sup> Laboratoire de Chimie Pharmaceutique, Université de Liège, 1, Avenue de l'Hôpital, B-4000 Liège, Belgium

<sup>f</sup> Inserm Univ 045131, EA1046, Pharmacologie, Faculté de Médecine, Pôle Recherche, Université de Lille 2, 1, Place de Verdun, F-59045 Lille Cedex, France

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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; PPAR $\gamma$ ; 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

**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.

\* Corresponding author. Tel.: +33 (0) 676 06 10 85; fax: +33 (0) 320 44 53 93.

E-mail address: vamecq@lille.inserm.fr (J. Vamecq).

of the glitazone series such as rosiglitazone (Fig. 1). More especially, 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



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