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Development of docking-based 3D-QSAR models for PPARgamma full agonists

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ABSTRACT

Peroxisome proliferator-activated receptor gamma (PPARγ) has become an attractive molecular target for drugs that aim to treat diabetes mellitus type II, and its therapeutic potency against skin cancer and other skin diseases is also currently being explored. To study the relationship between the structure of several PPARγ full agonists and the trans-activation activity of PPARγ, we have performed a three-dimensional quantitative structure–activity relationship (3D-QSAR) study of tyrosine-based derivatives, based on the 3D alignment of conformations obtained by docking. Highly predictive 3D-QSAR models, with Pearson-*R* values of 0.86 and 0.90, were obtained for the transactivation activity and binding affinity of PPARγ, respectively. These models are in good agreement with the structural characteristics of the binding pocket of PPARγ and provide some structural insights for the improvement of PPARγ full agonist bioactivities.

1. Introduction

Peroxisome proliferator-activated receptors (PPAR) are fatty acid-activated transcription factors that belong to the nuclear hormone receptor family [1,2]. Three PPAR isotypes, PPARα, PPARβ/δ and PPARγ, have previously been identified. Each of these subtypes appears to be differentiated in a tissue-specific manner and plays a pivotal role in glucose and lipid homeostasis [3,4]. PPARγ constitutes a primary target for the development of drug candidates for the treatment of type II diabetes. Thiazolidinediones (TZDs) represent the first known PPARγ agonists used as oral antidiabetic agents [4,5]. In addition, several studies have suggested that oral PPARγ full agonists not only exert an antidiabetic effect but also may act as a promising therapeutic target for a broad variety of skin disorders, including inflammatory skin diseases, such as psoriasis and atopic dermatitis, melanoma and other skin malignancies [6–9]. Furthermore, PPARγ full agonists may even induce cell growth arrest, apoptosis and terminal differentiation in various human malignant tumors [7]. There are several synthetic PPARγ full agonists besides TZDs with high potency and selectivity [10–14].

Over the past decade, a number of protein structures of the PPARγ ligand-binding domain (LBD), co-crystallized with ligands or in the apo-form, have been resolved by X-ray crystallography [4,15]. The binding pocket of PPARγ is very large and has a Y-shaped form, consisting of an entrance (arm III) that branches off into two pockets [16]. Arm I is extended toward H12, and arm II is situated between helix H3 and a β-sheet [16]. Arm I is the only substantially polar cavity of the PPARγ LBD, whereas arms II and III are mainly hydrophobic. To show biological activity, only two arms need to interact with the ligand; therefore, PPARγ full agonists occupy arms I and II [17].

It is expected that the use of quantitative structure–activity relationship (QSAR) approaches could correlate the observed biological activities with structural changes of the ligands [18]. Although several QSAR models for PPARγ full agonists have been performed [19–24], some of them used a small series of ligands, analyzed only the binding affinity or the trans-activation activity or developed 2D-QSAR models. We have constructed two atom-based 3D-QSAR models, one for the binding affinity and another for the transactivation activity, that use poses obtained by docking to align the structures of a set of tyrosine-derivate PPARγ full agonists. The additional advantages of our procedure are that we take into account the structures of both the ligands and the receptor and that a comparison of the binding affinity and transactivation activity

Abbreviations: LBD, ligand binding domain; PPAR, peroxisome proliferator-activated receptor; QSAR, quantitative structure–activity relationship; SAR, structure–activity relationship; TZDs, thiazolidinediones.

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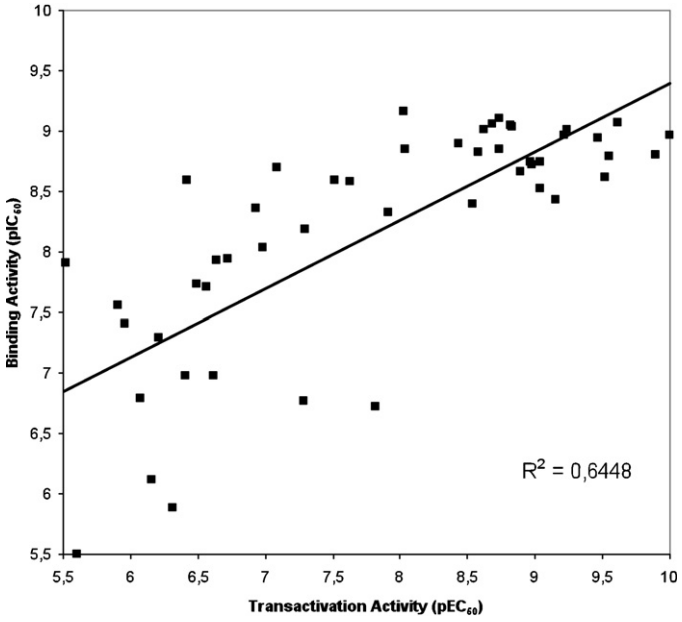

Fig. 1. Correlation between the experimental transactivation activity and experimental binding activity of the 49 tyrosine-based PPARγ full agonists used for the construction of the 3D-QSAR models.

models may provide some structural insights of the features needed by full agonists to increase the trans-activation activity of PPARγ. We have applied a similar procedure to the analysis of the structural insights of PPARγ partial agonists [17].

2. Materials and methods

2.1. Datasets

A dataset of 49 tyrosine-based compounds with measured pK_i (*i.e.*, binding affinity) and pEC_{50} (*i.e.*, transactivation activity) values obtained from the same laboratory [10–12] was used to generate two 3D-QSAR models (see Supporting Information Figure 1). The chemical structures of these 49 compounds are unequivocally known (*i.e.*, there are either no chiral atoms in their structure or the chirality of the molecules is defined), their pEC50 and pK_i values span six and five orders of magnitude, respectively, and each order of magnitude is represented by several compounds. Of the 49 molecules, 25 were randomly assigned to the training set, whereas the remaining 24 molecules were assigned to the test set. An additional set of 45 tyrosine-derivative compounds [10–12], 6 thiazolidinediones [10] and 68 indanyacetic acid derivates (for which only pEC_{50} values were available) [14] were used as an external validation set (see Supporting Information Figures 2–4). Because the measured pK_i and pEC_{50} values for the set of 45 tyrosine-derivative compounds were for a racemate solution of these compounds, not for the enantiomerical pure compounds, we added 0.3 (*i.e.*, log10 2) to all measured pK_i and pEC_{50} values of these compounds. This is equivalent to assume that the concentration of a racemate required to obtain a certain effect is twice the concentration of the corresponding active enantiomer [24]. All compound structures were built with ChemDraw Ultra v11.0 (CambridgeSoft Corporation, Cambrigde, MA, USA; http://www.cambridgesoft.com), and their 3D structures were further minimized with the LigPrep v2.4 program (Schrödinger LLC., Portland, USA; http://www.schrodinger.com), using the OPLS_2005 force field at pH 7.0 and the rest of the parameter values by default.

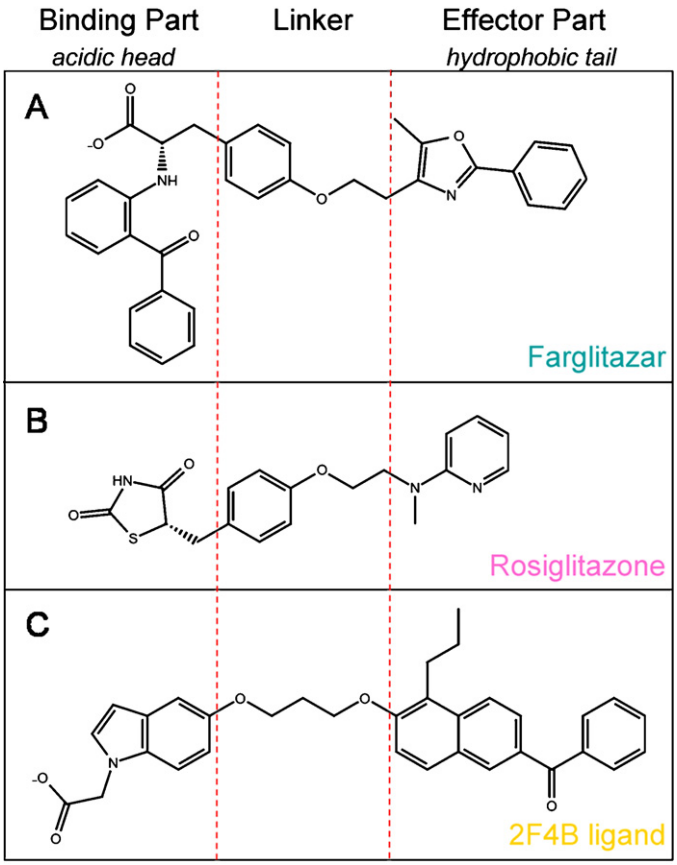

Fig. 2. Schematic representation of the common parts of PPARγ full agonists.

2.2. Molecular alignments

The most crucial step for a 3D-QSAR construction model is the alignment of the molecules. We chose a structure-based docking strategy that was carried out using the poses predicted by docking using the Glide v5.6 program (Schrödinger LLC., Portland, USA; http://www.schrodinger.com). All tyrosine-based PPARγ full agonists were docked within the binding site of the 1FM9 structure. Meanwhile the 6 thiazolidinediones and the 68 indanyacetic acid derivates used as an external set were docked within the binding sites of the 1FM6 and 2F4B structures, respectively. The binding site was defined using the *Receptor Grid Generation* panel with the default options. Standard-precision (SP) docking was selected for screening the ligands. We selected the flexible docking mode, in which the Glide program generates conformations internally during the docking process. We did not request any constraint for docking. Each docking run generated at most twenty poses per ligand that survived the post-docking minimization process. The GlideScore was used as a function of fitness. The best scoring pose was selected for each ligand and used as an input structure for the subsequent 3D-QSAR analysis.

2.3. Generation of the 3D-QSAR models

The selected conformations of the ligands, obtained with the previously described alignment protocol, were used for the generation of two 3D-QSAR models, one for pIC50 and the other for pEC_{50}. The Phase v3.2 program (Schrödinger LLC., Portland, USA; http://www.schrodinger.com) was utilized for constructing the 3D-QSAR models. These models can be atom-based (where all of the atoms of each ligand are taken into account) or