Structural Basis for the Design of PPAR-γ Ligands: A Survey on Quantitative Structure- Activity Relationships

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Abstract: The present review after providing a short overview on PPARs and their pleiotropic action focuses on the QSAR studies reported mainly for PPAR-γ agonists. The different 3D and 2D QSAR models are discussed, their impact in better understanding of the mechanism of action is analyzed and their contribution in the design of new molecules is outlined.

Key Words: PPAR-γ, type II Diabetes, mechanism of action, 3D-QSAR, 2D-QSAR, drug design.

INTRODUCTION

The isotype-γ of Peroxisome - Proliferator Activated Receptor PPAR-γ is a nuclear receptor, which constitutes a primary target for the development of drug candidates for the treatment of type II diabetes [1-3]. According to WHO, type II diabetes has reached epidemic proportions, with high and rapidly escalating prevalence [4,5]. Therefore, during the last fifteen years PPAR-γ research has attracted increasing interest counting more than 5000 records in PubMed database. On one hand, such research efforts are oriented to the characterization of the receptor and elucidation of its function at the transcriptional level and on the other hand to the design and synthesis of ligands capable to activate its transcriptional activity. QSAR methodology is a useful tool that can serve in rationalizing ligand design and in analyzing in a systematic way the information incorporated in the available data [6-9]. In the field of PPAR-γ as drug target, a number of relevant studies have appeared in literature concerning binding affinity and gene transactivation. In fact, in PPAR-γ research Quantitative Structure-Activity Relationships have been developed in parallel with the progress on structural and biochemical rationalization of the receptor activation, with both approaches interacting and validating the assumptions for binding requirements. The present review provides a short overview on PPARs and their pleiotropic action, focuses on the QSAR studies reported mainly for PPAR-γ agonists and attempts to analyze their impact in better understanding of the mechanism of action and in the design of new molecules.

THE PPARs- A SHORT OVERVIEW

Peroxisome - Proliferator Activated Receptors (PPARs) belong to the nuclear hormone receptor superfamily, initially described as molecular targets for compounds, which induce peroxisomal proliferation [10-12]. To date, three different isotypes of PPARs have been identified in various species: PPAR-α, PPARβ/δ and PPARγ [13-15]. Each of these subtypes appears to be differentiated in a tissue-specific manner and to play a pivotal role in glucose and lipid homeostasis. PPAR-α is primarily associated with lipid metabolism and its activation leads in decrease of triglyceride levels and increase of cardioprotective HDL cholesterol levels [16]. PPAR-α agonists have been shown to prevent the development of cardiac hypertrophy and left ventricular dysfunction [17]. Furthermore, PPAR-α ligands have shown beneficial effects in reducing myocardial infarction by attenuating oxidative stress, apoptosis and inflammation [18]. PPAR-δ is less investigated and may be related with dyslipidemia, obesity and wound healing [19]. Ongoing studies have demonstrated the role of PPAR-δ in ameliorating cardiovascular complications. PPAR-δ agonists have been shown to reduce the expression of inflammatory mediators and adhesion molecules, suggesting their potential role in attenuating atherogenesis [20-22]. The most extensively studied isoform, PPAR-γ, is predominantly expressed in brown and white adipose tissues and plays a central role in the process of adipocyte differentiation and peripheral glucose utilization, improving insulin sensitivity [23,24]. Beyond lipid metabolism, lipid storage and glucose homoeostasis, it is also associated with a wide spectrum of other actions such as cell differentiation, cell cycle regulation, apoptosis, carcinogenesis, inflammation, atherosclerosis and bone metabolism [25-31]. Currently, it offers a molecular target mainly for drugs developed for the treatment of type II diabetes mellitus [1-3], while its therapeutic potency against cancer disease is currently being explored in preclinical studies [32]. Recently considerable interest has been oriented in combining the beneficial effects of PPAR-α and PPAR-γ activation, in order to circumvent side effects including weight gain, fluid retention and edema so that a tailored therapy of type II diabetes to be achieved [33-37]. Moreover ongoing research programs are focused on the investigation of pan-agonists, looking to combine the potential effects of PPAR-α, γ and δ agonists [38, 39]. Partial PPAR-γ agonists are also being developed as a promising alternative, considering that they

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may retain the beneficial effects while diminishing the adverse effects [40, 41].

THE PPAR – γ RECEPTOR AND ITS LIGANDS

PPARs pleiotropic action is triggered upon binding with a small lipophilic ligand, followed by a conformation change and heterodimerization with another nuclear receptor, the retinoid X receptor (RXR). The heterodimer binds to specific consensus DNA sequences, known as peroxisome proliferators responsive elements (PPREs) which are located in upstream of responsive genes, inducing an increase in gene transcription [42-44]. Natural ligands which activate the PPAR-γ are several unsaturated fatty acids, in particular prostaglandins (15d-PGJ2) and nitrolinoleic acids, which display activity at micromolar concentration level [45-47].

The first PPAR-γ crystal structure was resolved in 1998 with rosiglitazone, a thiazolidinedione derivative, as the bound ligand [48]. Nowadays a number of protein structures of the PPAR Ligand Binding Domain, co-crystallized with ligands or in the apo-form, with or without co-activator, have been solved by X-ray crystallography and are available in the Protein Data Bank [49-53]. The overall structure is common to all three isotypes of PPAR LBD and resembles the LBDs of other nuclear receptors [54, 55]. A particular feature of ligand binding site in PPARs is the very large cavity within the protein with a total volume of 1300-1400 $Å^3$, substantially larger than in other nuclear receptors [56]. The cavity is Y-shaped and includes an entrance, extending from the surface of the protein and then branching to two arms, each approximately 12 Å in length, Fig. (**1**). The binding site entrance is very flexible and can potentially adapt, allowing large ligands to enter the binding pocket without significantly changing the overall structure of the LBD [57, 58]. Arm I is the only region with polar residues, which form part of a hydrogen-bond network involving the carboxylic group of fatty acids upon binding. The hydrophobic arm II and the hydrophobic part of the entrance are occupied by the hydrophobic tail. Due to the large size of the cavity and the flexibility in the hydrophobic entrance, the hydrophobic tail is in equilibrium between different positions [57].

A similar interaction network may exist in PPAR complexes with synthetic ligands [57-59]. 3D-QSAR methodologies have been effectively employed to recognize pharmacophoric units with crucial interactions for the ligand, as will be described in the next section. According to such studies and empirical structure-activity relationships typical PPAR-γ agonist molecules usually possess an acidic head involved in the hydrogen bond network, a central aromatic moiety and a hetero-aromatic hydrophobic tail as illustrated in Fig. (**2**). This topology is maintained in a large number of synthetic PPAR-γ ligands, which belong mainly to five chemical classes: thiazolidinediones (TZDs), tyrosine-based (TB), indole-based, propionic-acid and phenylacetic acid derivatives.

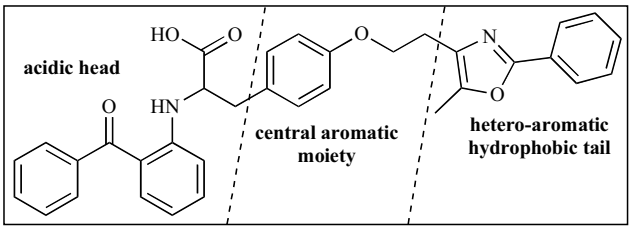

Fig. (2). The structure of a typical PPAR-γ agonist (farglitazar) divided into three substructures according to essential pharmacophore elements, which comprise an acidic head linked to central aromatic moiety and a hetero-aromatic hydrophobic tail.

In Fig. (**3**) the structures of eicosanoic acid and some representative PPAR-γ synthetic ligands are depicted. In the case of chiral compounds in early studies the S-enantiomers proved to be the eutomers [60, 61]. TZDs represent the first known PPAR- γ ligands, synthesized as oral anti-diabetic agents [62-64]. Some of them are marketed drugs (pioglitazone and rosiglitazone) for the treatment of type II diabetes mellitus [15], while netoglitazone is in Phase II and III clinical trials [65]. The tyrosine analogs constitute the largest chemical class, attracting further interest as a result of the toxic side effects reported for TZDs [66, 67]. Among them, the dual α/γ agonists, tesaglitazar and farglitazar, belonging to the glitazars subgroup, reached clinical trials but their development was discontinued, while chiglitazar is currently under Phase II [68]. Recently, the population of the indole based category of PPAR-γ agonists tends to increase, since the indole nucleus is recognized as a privileged drug-like scaffold [69-73].

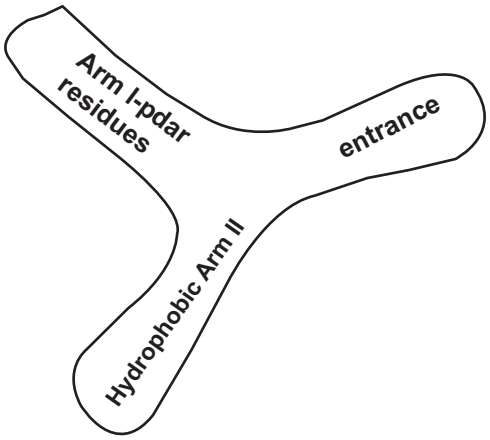

Fig. (1). A schematic representation of PPAR receptor cavity.

QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS

The discovery of new PPAR-γ ligands as drug candidates, as well as the understanding of the mechanism of action and the identification of the pharmacophoric features, have been substantially supported by relevant QSAR studies. In principle these studies follow two different strategies. One strategy considers the three dimensional structures of ligands constructing CoMFA, CoMSIA, or x-D QSAR models through careful alignment. The other strategy uses a large pool of descriptors to derive 2D-QSAR models by multiple linear regression or multivariate data analysis. The first type of models are valuable for pharmacophore mapping and rationalization of the design of new lead compounds, while the latter are more informative on molecular factors governing activity and could serve as a guide for further lead optimization.

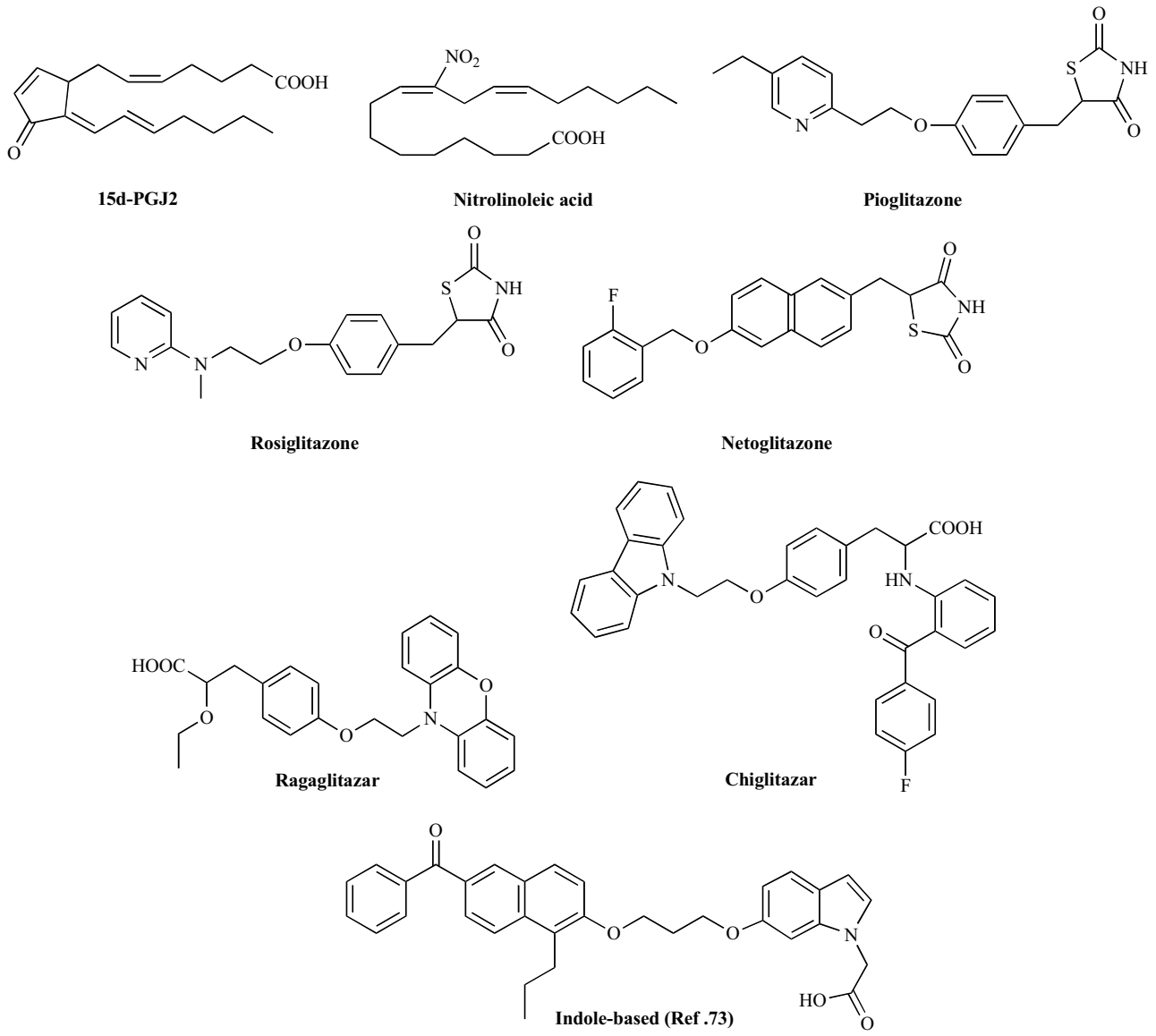

Fig. (3). Representative natural and synthetic PPAR-γ agonists belonging to different chemical classes.

In the case of PPAR-γ ligands, 3-D QSAR studies are mostly reported in literature , reflecting the need that still remains for improving the understanding of the mechanism of action and the demand for new chemotypes with improved potency as lead compounds. For a better comprehension of these models and in order to evaluate their contribution in PPAR research, a short account on the underlying background of the applied methodology will be given.

3-D QSAR FOR PPAR-γ LIGANDS

Comparative Molecular Field Analysis (CoMFA), generally regarded as the industry standard for constructing three-dimensional Quantitative Structure-Activity Relationships (3D-QSAR) models, is particularly effective in cases when there is not enough information on the targeted receptor. The CoMFA method was developed by Cramer in 1988 and is based upon the calculated energies of steric and electrostatic interactions between a hypermolecule obtained by superimposing a set of ligands and a probe atom placed at the nodes of a regular 3-D lattice [74, 75]. The model is subsequently developed by partial least-squares analysis (PLS) and used to predict the activity of new compounds. Correlation coefficients R^2 and cross validated correlation coefficients Q^2 are the statistics proving the quality of the models, while the use of a test set to further validate their predictive ability is a necessary requirement for such studies. One advantage of CoMFA is the graphical representation of the results of the analysis as 3-D grids where the steric and electrostatic contributions of the activities are displayed. However the fields used in CoMFA imply some shortcomings. The Lennard-Jones and Coulomb potentials show singularities at the atomic positions and cutoff values must be defined in order to avoid unacceptably large values. Furthermore the Lennard-Jones potential is very steep close to the van der Waals surface and consequently the potential energy in the proximity of this region changes dramatically and is strongly affected by small mutual shifts of the superimposed molecules or minor conformational changes.

The first CoMFA model in the PPAR-γ field appeared in 1999. Kulkarni *et al.* analyzed 53 thiazolidinediones using *in vivo* biological data [76]. The hypoglycaemic activities of the compounds was expressed as the negative logarithm of the effective molar dose required to reduce blood glucose by 25% pED_{25} in genetically obese and diabetic yellow KK mice. After repeated alignments the authors obtained models which exhibited satisfactory statistics ($0.689< R^2<0.921$ and $0.624 <Q^2 <0.764$). Steric and electrostatic fields were found to contribute almost to the same extent to the activity. The introduction of calculated lipophilicity (clogP) as additional descriptor did not improve the model, although in a limited study of benzyloxazolidine-2,4-diones a correlation between lipophilicity and potency was reported with the latter increasing as logP increased [63]. The CoMFA contour maps were used to propose a hypothetical receptor model, which was in agreement with the results from the crystal structure of thiazolidinedione available by then [48].

Next to CoMFA, Comparative Molecular Similarity Indices Analysis (CoMSIA) is an analogous powerful 3-D QSAR technique [77, 78]. Instead of interaction fields it calculates similarity indices using a distance-depended Guassian functional form. Five types of similarity indices, steric, electrostatic, hydrophobic, and hydrogen-bond donor and acceptor are calculated, using a common probe atom with 1 Å radius and a value +1, for charge, hydrophobicity, hydrogen-bond donor and acceptor properties. The obtained indices are evaluated in a PLS analysis as in the CoMFA protocol. The graphical representation of contour maps in CoMSIA highlights the areas within the region occupied by the ligands, that 'favour ' or 'dislike ' the presence of a structural feature with a given physico-chemical property and in this sense they are more easily interpretable than CoMFA contour maps [77]. Another advantage of CoMSIA over CoMFA technique is its greater robustness regarding small mutual shifts of the superimposed molecules or minor conformational changes, thus being less alignment- depended, while there is no need for arbitrary cutoffs and indices can be calculated at all grid-points.

Liao *et al.* used both CoMFA and CoMSIA to derive QSAR models for a data set of 74 tyrosine analogs including also 5 thiazolidinediones [79]. The activity was expressed at the molecular level as binding affinity (pK_i). The CoMSIA model was more informative showing the considerable contribution of hydrophobicity indices to binding affinity. The crucial hydrogen bond acceptor role of the oxygen atom, which serves as a bridge between the aromatic central moiety and the heterocyclic tail, was revealed by the involvement of the relevant similarity indices. In the corresponding CoMFA model steric fields dominated. The importance of hydrogen bonding associated with the acidic head was further investigated by the same authors using Eigenvalue Analysis for the same data set [80].

Eigenvalue analysis (EVA) provides conformational sensitive but superposition-free descriptors, characterized also as 2½ D, which have been shown to perform well in modelling biological end points [81, 82]. EVA is derived from calculated infrared-range vibrational frequencies using an input molecule that is energy minimized. EVA QSAR model uses 2D plots to facilitate interpretation in a fashion similar to that used to interpret an experimental IR spectrum e.g. by examination of the distribution of vibrations in a molecule or in a set of molecules. As with real infrared spectroscopy, EVA profiles of a compound are divided in the fingerprint region (1-1500 cm^{-1}) and the functional group region (1500-4000 cm^{-1}). The latter contains specific information and can be correlated with the activity regarding the presence or absence of particular functional groups.

In the EVA QSAR model reported for PPAR-γ binding affinity [80] the functional group region showed prominent peaks in the hydrogen bond stretching frequency region (at about 3200 cm^{-1}), for the tyrosine-based compounds, which possess two hydrogen bond donor sites, i.e., the carboxylic OH group and the NH group. For the TZD analogs the peak of the hydrogen bond donor was attenuated because there is only one hydrogen bond donor in those molecules. The authors formulated the assumption that the stronger activity of the tyrosine analogs compared to TZDs should be attributed to the higher number of hydrogen bonds they form as donors. In addition, the bulk substitution on the tyrosine nitrogen atom may also contribute to the higher affinity interacting with an area of the ligand-binding domain of PPAR-γ that is not accessible to the TZDs. The statistical data of the models depended on the Hamiltonians used to calculate normal modes of vibrations, with R^2 and Q^2 values up to 0.920 and 0.587 for the AM1 method and 0.863 and 0.586 for the PM3 method respectively, for the training set. The predictive ability was further validated for a test set with the best predictive R^2 value of 0.614 for AM1 and 0.822 for PM3 methods. The bridge oxygen, the carboxylic carbonyl group as well as the electron density clouds over the bridge oxygen were identified as essential pharmacophore sites in a 3D QSAR study of tyrosine analogs using the logico-structural based approach (Apex-3D) [83]. This approach uses the molecular structures after energy minimization to derive certain physicochemical properties which are used by the Apex-3D software for automated identification of pharmacophores (biophores in the software), superimposition of compounds and quantitative model building [84, 85]. These pharmacophores can be regarded as the local array of descriptor centres, thus depending not only on the physicochemical properties of the 'biophoric' sites but also on their spatial arrangement in terms of mean 'biophoric' distances. The first study using the Apex-3D QSAR method on PPAR-γ ligands pertains a limited series of seven TZDs [86]. In a later publication 23 tyrosine analogs were modelled by this methodology [83].The oxygen atom and carbonyl group, identified as pharmacophore features, are electron-rich sites capable of donating electrons and may be involved in electrostatic, ionic and p–p interactions, while the electronic cloud on the oxygen atom may form hydrogen bonds with the receptor. Using these pharmacophore features as template for superimposition, two secondary pharmacophore sites were also suggested, one being located on the carbon atom of the phenyl ring attached to the acidic head and another on a carbon atom in the spacer between the lipophilic tail and the aromatic centre.

As mentioned in the introduction, the concept of dual PPAR-α/γ agonists has gained considerable interest in the last years and relevant 3D QSAR studies have been reported.

A CoMFA model was developed for a set of thiazolidinedione and oxazolidinedione derivatives with PPAR- α/γ dual activity, which was based on the assumption of the 'additivity' of fields [87]. In this sense biological activities for the individual receptors were added to get the combined activity for both receptors on which CoMFA was performed. The dual model was compared to independent CoMFA models derived for the PPAR-α and PPAR-γ activity of the compounds. It was clearly shown that the electrostatic fields contribute relatively more in the α –model, while the steric fields play an important role in the γ–model with large molecular regions, including the acidic head, favourable for bulkier groups. In the dual-model a proper balance between these field contributions was observed, confirming that the resulting fields represent 'additivity fields' which incorporate features of both receptors.

An analogous approach based on the 'sum of activities' was recently applied to derive a CoMFA model for panagonists, using a series of indanyl acetic acids, which showed moderate affinity for α, β subtypes and high affinity for the δ subtype. The 'sum-model' was used to design new molecules with better predicted 'overall activity' [88].

In all the above mentioned studies, compounds were considered as neutral molecules, whereas in physiological conditions the presence of deprotonated species should be anticipated. In addition the flexible entrance of the binding pocket renders the bioactive conformation rather ambiguous. These issues can be faced by *Quasar*—a quasi-atomistic receptor-modeling concept, a bridge between 3D QSAR and receptor modelling, which considers the impact of induced fit onto ligand binding [89, 90], while the most recently developed 6D-QSAR technology allows for the simultaneous consideration of different solvation scenarios of the receptor active site [91]. The *Quasar* concept has been used for the validation of quantitative structure–activity relationships for several biological systems of medicinal interest, including nuclear receptors and PPAR-γ among them. The study on PPAR–γ included the same series of 95 tyrosine analogs and 6 TZDs analysed previously by Liao *et al.* [79]. The authors represent the properties of the receptor surrogate model on a wire frame surface around the ligand. They refer to hydrophobic properties, hydrogen bond donor sites and hydrogen bond acceptor sites. The latter involve the acidic head which also participates in a salt bridge with positively charged receptor site. The model is accompanied by good statistics, a cross validated Q^2 =0.832 for the training test and predictive R^2 =0.723 for the test set, while it proved efficient to predict the binding constant K_i for three structurally different compounds.

2-D QSAR FOR PPAR-γ LIGANDS

The above described 3D-QSAR studies on PPAR have contributed substantially in the understanding of the factors which are crucial in ligand receptor interactions and in rationalizing the generation of lead compounds by identification of the essential structural characteristics. However they suffer from limitations concerning the ambiguity of the bioactive conformation and the difficulties associated with superposition. Hence, they are restricted to compounds that exhibit the most similar structure possible with the reference agonist. Moreover, even within congeneric compounds, the structural diversity increases as the data set increases, thus alignments become disputable. Therefore such studies are difficult and often time-consuming to be applied in a large data set.

On the other hand, the 2D-QSAR methods are not affected by alignment rules and/or assumptions on conformations and therefore they can easily be applied to large compound libraries compiled from different sources. Nevertheless, in this case the quality of the activity data should be attentively considered since small changes in the experimental protocol may affect the results.

Rücker *et al.* made a careful compilation of pK_i and pEC_{50} data for 177 PPAR-γ ligands and used them to develop 2-D QSAR models [92]. The data set comprised structural diverse compounds, the majority of which were tyrosine analogs. Some thiazolidinediones, indole derivatives, amino-propoxyphenoxy acetic acid derivatives, isopropoxy-phenylpropanoic acid derivatives as well as some natural fatty acids and thiazolidinedione-fatty acids hybrids were also included. The authors used a large number of descriptors including atom and bond counts, connectivity indices, partial charge descriptors, pharmacophore feature descriptors, calculated physical property descriptors like lipophilicity plus the MACCS keys, which represent bit string representations of structures, where each bit refers to the presence or absence of a unique substructural pattern [93]. The descriptors were calculated considering the protonation state of the compounds. Multiple linear regression analysis was applied to derive models for binding affinity as well as for the gene transactivation process expressed as pEC_{50} values. For binding affinity, models were derived for the whole data set and independently after partitioning the data into a training and a test set. Considering the structural diversity, correlation coefficients were satisfactory with R^2=0.79 and Q^2=0.76 and R^2=0.79 Q^2=0.74 for the training and test set, respectively. However the two models contained different descriptors sharing only 3 MACCS descriptors, one of them referring to the formal charge on carboxylate. Calculated lipophilicity of the neutral species was included with a positive sign in the model for the training set but not in the overall model. A positive effect of lipophilicity was also shown in the model generated for gene transactivation data. Nevertheless, the pEC_{50} model had inferior statistics with R^2=0.65 Q^2=0.57. The difficulties encountered in building up QSAR models for transactivation were attributed to the lower quality of experimental data, derived in cellular level and to the higher complexity of the biological processes involved. Therefore the authors suggested that pEC_{50} values may be better predicted from the pK_i values, if available, by means of an activity-activity model, which they constructed by introducing three additional descriptors in the pEC_{50}/pK_i relationship. To this point, it should be noted that in the described models, although characterised by the authors as portable and easy to use for predictions, not all the descriptors are easily understood. One important concern, highlighted in the paper, is the problem that a correlation found for the entire set of combined heterogeneous compounds, may vanish or be obscure within subgroups. In fact, predicted versus experimental pK_i values broken down to subgroups showed a rather poor pat-

tern for indole based derivatives, tyrosine based derivatives with reduced molecular weight and the TZD-fatty acid hydrids. This is an indication that the majority of tyrosine analogs drive the model towards a certain direction with the 6 TZDs well accommodated within the model, while for the remaining subgroups other factors, not incorporated in the model, may be important.

In a recent 2D QSAR study, concerning a limited series of only tyrosine analogs steric, electronic and topological descriptors were found to have important role in governing the variation in PPAR-γ agonistic activity, with the relative negative charge being the most important factor [94].

Multivariate data analysis has recently been applied as the statistical methodology to establish 2-D QSAR for tyrosine –based PPAR-γ ligands [95]. This type of analysis can treat a large number of interrelated descriptors exploiting the maximum information encoded within them [96, 97]. It is a projection method to latent variables, the Principal Components, which are linear combination of the original descriptors. Principal Component Analysis is further extended to a regression method through partial least squares projections to latent structures (PLS). PLS is used to connect the information in two blocks of variables, the descriptors X and the response variables Y.

In reference [95] the authors used a data set of the same 106 tyrosine analogs investigated by Rücker *et al.* [92] and a pool of whole molecule descriptors and descriptors referring to the three parts of the pharmacophore structure. Among the descriptors physicochemical and molecular properties, constituting druglike characteristics were included. The concept of druglikeness has been developed in an effort to avoid failure of drug candidate due to poor ADME properties [98, 99]. A two component PLS model was reported with R^2=0.82 and Q^2=0.78. Molecular size and surface parameters exerted considerable positive influence in binding. Lipophilicity and flexibility (expressed as the number of rotatable bonds) contributed positively but at a lesser extent to the model. A number of substructural descriptors had also to be included in the model. For gene transactivation pEC_{50} data the authors obtained less significant models. However they reported a satisfactory two component model for the 22 highly active compounds with R^2=0.89, Q^2=0.78, (pEC_{50} range: 8.5-10).

The same authors extended their investigations to a data set of 109 indole-based derivatives with available pK_i values and using multivariate data analysis they established a three component PLS model with R^2 =0.82, Q^2 =0.80 [100]. In this case, lipophilicity proved to be the most important descriptor, followed by molecular weight, both with a positive influence. Flexibility and non polar surface parameters exerted a negative effect, an indication that indole based PPAR–γ agonists should be more rigid and compact molecules, compared to the tyrosine analogs. Moreover electrophilicity was found to be another important factor for PPAR–γ binding affinity of indole derivatives, while not included in the tyrosine model [95]. The high demands for both lipophilicity and molecular weight in the case of indole derivatives should be carefully considered in further design, since they could lead to a violation score of 2 concerning the widely accepted 'rule-of-five' for oral bioavailability [99]. To this purpose, it should be noted that a survey on druglike characteristics of a large number of PPAR-γ ligands showed that 40% of active compounds (pEC_{50}>7) violate the 'rule-of-five' in respect to lipophilicity and molecular weight [101]. In an analogous study on mostly tyrosine and TZD analogs it was shown that high activity can be achieved with moderate lipophilicity [102].

A 2D QSAR on dual PPAR α/γ activity data of some 2-alkoxydihydrocinnamates has recently appeared in literature. The authors found that electronic properties of the substituents in the phenyl ring of the hydrophobic tail play a key role, while bulky substituents in the acidic head do not confer selectivity towards the PPAR activity [103].

CONCLUSIONS AND PERSPECTIVES

PPAR-γ agonists represent a paradigm where synthesis of new chemotypes, X ray crystallography and QSAR studies advance in parallel and interactively. 3D-QSAR proved efficient in providing models with interaction fields in reasonable agreement with those deduced by the crystal structure of receptor-ligand complexes, so that pharmacophore requirements are well established. The progressive diversity in the PPAR-γ ligands, with new chemical classes being developed, challenged the establishment of general 2D-QSAR models. However special trends within each class seem to exist and need further exploration. Due to the high demands on molecular size and lipophilicity, consideration of druglike characteristics in parallel with binding affinity in a more holistic approach may be a necessity in the design of optimized structures, so that failure of drug candidates at a later development stage to be avoided. Another perspective is further exploitation of the potential beneficial effects of dual α/γ agonists or pan-agonists, by expanding the relevant QSAR studies towards that direction.

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