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ORIGINAL PAPER

Role of physicochemical properties in the activation of peroxisome proliferator-activated receptor δ

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Abstract Current researches on treatments for metabolic diseases involve a class of biological receptors called peroxisome proliferator-activated receptors (PPARs), which control the metabolism of carbohydrates and lipids. A subclass of these receptors, PPARδ, regulates several metabolic processes, and the substances that activate them are being studied as new drug candidates for the treatment of *diabetes mellitus* and metabolic syndrome. In this study, several PPARδ agonists with experimental biological activity were selected for a structural and chemical study. Electronic, stereochemical, lipophilic and topological descriptors were calculated for the selected compounds using various theoretical methods, such as density functional theory (DFT). Fisher's weight and principal components analysis (PCA) methods were employed to select the most relevant variables for this study. The partial least squares (PLS) method was used to construct the multivariate statistical model, and the best model obtained had 4 PCs, q^2=0.80 and r^2=0.90, indicating a good internal consistency. The prediction residues calculated for the compounds in the test set had low values, indicating the good predictive capability of our PLS model. The model obtained in this study is reliable and can be used to predict the biological activity of new untested compounds. Docking studies have also confirmed the importance of the molecular descriptors selected for this system.

Keywords *Diabetes mellitus* · Docking studies · Drug design · Metabolic syndrome · Molecular modeling · PPARδ · Theoretical methods

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Introduction

Diabetes mellitus (DM) and metabolic syndrome are two diseases that express common symptoms and decrease quality of life. DM is associated with the metabolism of carbohydrates while metabolic syndrome is related to the metabolism of lipids [1–7]. One of the biggest risk factors for both DM and metabolic syndrome development is insulin resistance and obesity, which occurs due to an alteration in carbohydrate and lipid metabolism and can lead to additional complications, such as atherosclerosis, and hypertension [5–10].

A class of biological receptors called peroxisome proliferator-activated receptors (PPARs) is involved in the control of the metabolism of carbohydrates and lipids. PPAR family has the isoform δ that, when activated, stimulates the lipid metabolism, as well as decreases the insulin resistance. Therefore, substances that activate this

subtype of PPAR should be studied as future drug candidates to treat several diseases, such as metabolic syndrome [5, 11–20]. One strategy that can be used to design new therapeutic agents is to employ molecular modeling techniques. Structure-activity relationship and quantitative structure-activity relationship studies have been carried out successfully with the aim of constructing multivariate statistical models that correlate chemical properties and biological activities of distinct classes of bioactive substances [21–27]. The main objective of this work is to use theoretical, multivariate statistical and docking methods to study the relationships between the atomic and molecular properties and the biological activity of a series of compounds that are potential drug candidates for the treatment of DM type 2 and metabolic syndrome, as well as understand the possible molecular basis responsible for the biological activity presented by the compounds studied.

Data set

From the compounds synthesized by Wickens et al. [28], we have selected 35 molecules to constitute the training set. Ten compounds were inserted into the test set (external validation) regarding the structural diversity and the range of biological property values, as is illustrated in Fig. 1. Table 1 displays the chemical structures and the biological activity values (EC_{50}) for all the compounds studied. The values of EC_{50} were measured under the same experimental conditions [28] and converted to the corresponding pEC_{50} ($-\log EC_{50}$), which were used as dependent variables in the multivariate analyses.

Geometry optimization

To perform all multivariate analyses, it is necessary to obtain the electronic, lipophilic, stereochemical and topological properties of the selected compounds. We first constructed the molecular structures of the compounds using Gaussview [29]. To select the best theoretical method to optimize these structures, we compared the RMS fit errors between the optimized and crystallographic (PDB code 3D5F [30]) geometries of the ligand L41 ({4-[3-(4-acetyl-3-hydroxy-2-propylphenoxy) propoxy]phenoxy}acetic acid). We also selected the most potent compound of the data set (compound 17) and compared its optimized geometries using AM1, PM3, B3LYP/6-31G* and B3LYP/DGDZVP to the crystal structure of L41. All calculations were performed using the molecular modeling package Gaussian03 [31]. The results obtained are presented in Table 2 and Fig. 2.

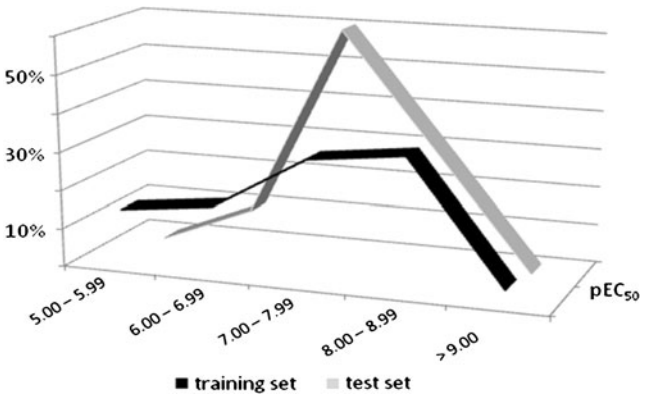


Fig. 1 Distribution of pEC_{50} values for training and test set

From Table 2, we see that the RMS fit errors from comparing the crystallographic structure of L41 to the optimized structures of compounds L41 and 17 are smallest for geometries obtained with B3LYP/6-31G* and B3LYP/DGDZVP, respectively. The structures displayed in Fig. 2 indicate that there was a perfect superposition of the phenoxy ring in both cases. However, the RMS fit errors obtained from the comparison of the crystallographic structure of L41 to the optimized structures of compound 17 are greater than those obtained by comparing the crystallographic structure of L41 to the compound's optimized structures. This is because compound 17 has different substituent groups than compound L41. Since the method employing the functional B3LYP [32, 33] and DGDZVP [34, 35] basis sets has yielded molecular structures that are in good agreement with the crystallographic geometry of a ligand (L41), we used B3LYP/DGDZVP to obtain the optimized structures of the other compounds.

Calculation of atomic and molecular properties

After the geometry optimization, atomic and molecular properties of all compounds were obtained. Electronic properties were calculated using Gaussian03 and the same method employed in the geometry optimization (B3LYP/DGDZVP). Stereochemical and lipophilic properties were calculated using the "QSAR" module in the molecular package HyperChem [36]. Several topological indices were also obtained using the software Dragon 2.1 [37]. Table 3 lists the electronic, stereochemical, lipophilic and topological properties employed in this study and Fig. 3 displays the numbering system we used.

Variable selection and multivariate statistical analyses

We initially calculated 1504 properties. To select the most relevant ones for our analyses, we used Fisher's weight values (W_F), which indicates the discriminating powers of the variables, and the principal component analysis (PCA). Variables that presented insignificant values of W_F ($W_F <$

Table 1 Chemical structures and EC_{50} values of the compounds studied [28]

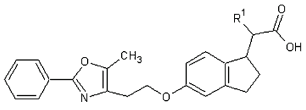
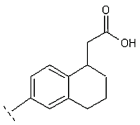
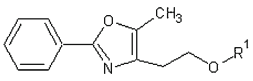
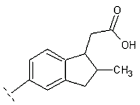
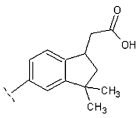
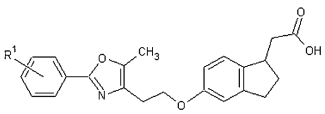
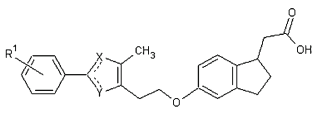
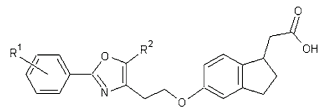
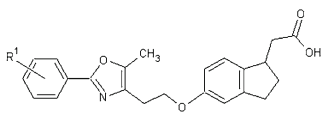
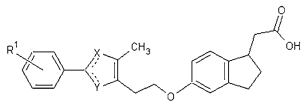
Cpd	General Structure	R^1	R^2	X	Y	EC_{50} (nM)
		Training set				
1		H	-	-	-	27
2		CH_3	-	-	-	120
3		CH_2CH_3	-	-	-	590
4		OCH_3	-	-	-	4400
5			-	-	-	3140
6			-	-	-	883
7			-	-	-	6480
8		4-OCH_3	-	-	-	3
9		3-OCH_3	-	-	-	18
10		4-t-Bu[a]	-	-	-	21
11		4-i-Pr[b]	-	-	-	1
12		3-F	-	-	-	13
13		4-CH_3	-	-	-	4
14		3-CN	-	-	-	73
15		4-Cl	-	-	-	3
16		H	-	S	N	11
17		4-CH_3	-	S	N	0.8
18		3,4-OCH_2O	-	S	N	5
19		4-OCH_3	-	S	N	4
20		3-OCH_3	-	S	N	61
21		4-F	-	S	N	7
22		2-F	-	S	N	116
23		4-Cl	-	S	N	1.5
24		3-OCH_3	-	S	N	272
25		4-OCF_3	-	S	N	2
26		4-Ph[c]	-	N	NCH_3	28
27		4-Et[d]	-	N	NCH_3	31
28		4-Et	-	NCH_3	N	347
29		4-OCH_3	-	N	NCH_3	86
30		4-OCH_3	-	NCH_3	N	10000
31		H	-	NCH_3	N	10000

Table 1 (continued)

32		H	Et	-	-	7
33		4-CH_3	Et	-	-	5
34		4-Et	Et	-	-	11
35		H	Pr	-	-	10
		Test set				
36		H	-	-	-	14
37		4-Et	-	-	-	3
38		4-F	-	-	-	7
39		4-Ph	-	-	-	6
40		3-CH_3	-	-	-	64
41		4-CN	-	-	-	35
42		3-Cl	-	-	-	13
43		3-F	-	S	N	47
44		3-CF_3	-	S	N	30
45		H	-	N	NCH_3	257

[a] t-Bu=$C(CH_3)_3$; [b] i-Pr=$CH(CH_3)_2$; [c] Ph=C_6H_{11}; [d] Et=CH_2CH_3

0.20) were discarded in our multivariate analyses, leaving 25 properties. Performing PCA on these 25 properties narrowed the selection down to the final seven variables used in our study (Table 3).

After the variable selection, we performed multivariate statistical analyses to obtain a statistical model to investigate the relationship between the atomic and molecular properties and the biological activity of the compounds under study. For this, we used the multivariate statistical method called partial least squares (PLS), which is implemented through the computational package Pirouette [40]. We autoscaled the variable set to give each of them the same importance. We selected the best model from PLS based on statistical parameters such as the values of PRESS (prediction residues error squares sum) and SEV (standard error of validation) and the optimum number of principal components (PCs). The quality of the model was evaluated by the cross-validation (leave-one-out) and calibration coefficients q^2 and r^2, respectively, and by the residues of prediction obtained from external validation (test set).

Table 2 RMS fit errors from comparing optimized geometries of compounds 17 and L41 to the crystallographic structure of L41 (PDB code: 3D5F)

Compound	AM1	PM3	B3LYP/6-31G*	B3LYP/DGDZVP
RMS fit error (Å)				
17	1.4577	1.5129	1.4540	1.3076
L41	1.3502	1.3511	0.1255	0.1398

Docking analyses

Using the docking program Surflex, implemented in the computational package Sybyl 8.1 [41], we have docked two compounds of the series (the most active - 17 and the least one - 30) using a crystallographic PPARδ structure (PDB code 3GZ9 [42]). This protein structure was selected based on the best resolution (2.00 Å) and due to the chemical similarity of its ligand to ones studied in this work. The docking studies were performed using the default parameters related to the rigid protein and flexible ligand, implemented in the program Surflex.

Results and discussion

The values of the seven properties studied (electronic, stereochemical, lipophilic and topological ones), along with the pEC_{50} values, are shown in Table 4 and the correlation matrix of the descriptors selected is presented in Table 5.

Using the seven atomic and molecular properties displayed in Table 4, we carried out PLS analyses. The optimum number of PCs was four because the PLS model with 4 PCs presented low values of PRESS and SEV and high values of q^2 and r^2 (q^2=0.80, r^2 = 0.90), indicating good internal consistency. Table 6 lists the statistical parameters that were used to select the best PLS model.

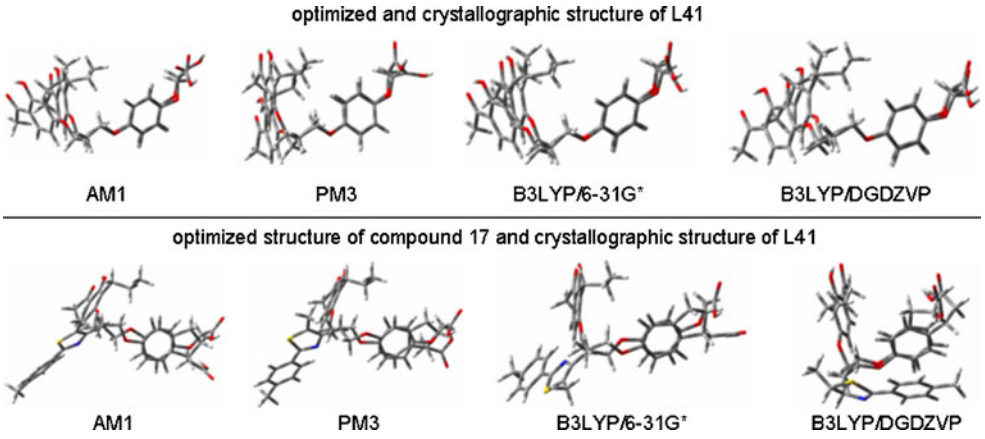


Fig. 2 Superposition of the optimized molecular structure of compound L41 with its crystallographic structure and superposition of the optimized molecular structure of compound 17 with the crystallographic structure of L41

From Table 6, we see that the best PLS model has good statistical parameters. The PLS equation that was attained after internal validation is:

$$pEC_{50} = 0.2086E_{LUMO} - 0.1979\,\mu - 0.4297V + 0.2496C_9 - 0.2631logP + 1.0419ATS7p + 0.2487AROM \quad (1)$$

Comparing our outcomes to those found by Giaginis et al. [43], which studied PPARγ ligands, we can verify that some molecular properties for PPARδ ligands studied in this work, such as LUMO energy, dipole and log P, are also important to PPARγ activation. This fact could be explained due to the high similarity of aminoacid residues in the active site of all PPAR isoforms [44]. Besides, our study indicates that other effects (stereochemical and topological) can influence the interaction between PPARδ ligands and the biological receptor.

Using this model Eq. 1, we predicted the biological activity (pEC_{50} values) of the compounds in the test set (external validation) and the results are listed in Table 7. A plot comparing the pEC_{50} values of the compounds in both the training and test sets obtained experimentally with those obtained with our model is shown in Fig. 4. There is good agreement between the experimental and calculated values for the compounds in the test set, indicating the reliability of the PLS model. The calculated pEC_{50} values were within 0.61 log units of the experimental values. Combined with the low residual values displayed in Table 7, we conclude that the PLS model we generated is reliable and can be used to accurately predict the biological activity of other compounds within this structural class.

After the construction and validation (internal and external) of the PLS model, we analyzed the chemical significance of the seven variables selected and their possible implications in the interaction between the PPARδ ligands and the biological target. We expected the variables to have good correlation with the biological activity (pEC_{50}) and thus indicate possible ligand-protein interactions, as described by Xu et al. [45], which discuss the most important interactions between a ligand and the PPARδ receptor. Some important findings were found, such as:

(1). The LUMO energy contributes positively to the model. Because the energy of the LUMO (lowest unoccupied molecular orbital) describes the electron-accepting character of a substance, this property is important to understand the charge transfer processes that occur when a ligand interacts with the biological receptor [46].

(2). Dipole moment has a positive contribution to the model and ATS7p has the most positive contribution.

Table 3 Selected properties and their definitions

Property	Type	Definition
E_{LUMO} (a.u.)	Electronic	Energy of the lowest unoccupied molecular orbital
μ (D)		Dipole moment
C_9 (a.u.)		Atomic charge at carbon 9, derived from electrostatic potentials (ESP)
V (Å^3)	Stereochemical	Volume
Log P	Lipophilic	Partition coeficient
ATS7p	Topological	Topological property related to atomic polarizability [38]
AROM		Aromaticity index [39]

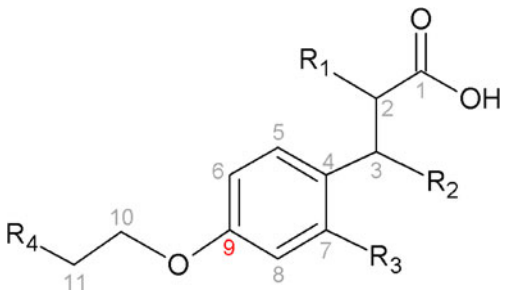


Fig. 3 General structure and numbering system used in this study

Table 4 Selected electronic, stereochemical, lipophilic and topological descriptors and pEC_{50} values for all compounds studied (training and test sets)

Cpd	E_{LUMO} (a.u.)	μ (D)	C_9 (a.u.)	V (Å^3)	Log P	ATS7p	AROM	pEC_{50}
Training set								
1	-0.0474	5.695	0.430	1120.49	3.03	0.431	0.995	7.57
2	-0.0445	3.304	0.412	1167.93	3.59	0.416	0.995	6.92
3	-0.0480	1.564	0.410	1201.65	3.98	0.403	0.995	6.23
4	-0.0532	3.443	0.445	1203.69	2.80	0.410	0.995	5.36
5	-0.0497	1.323	0.487	1153.45	3.42	0.416	0.994	5.50
6	-0.0488	3.414	0.415	1175.70	3.36	0.413	0.995	6.05
7	-0.0501	2.196	0.470	1202.51	3.79	0.410	0.995	5.19
8	-0.0436	1.550	0.400	1189.60	2.77	0.433	0.994	8.52
9	-0.0430	1.879	0.439	1185.08	2.77	0.423	0.996	7.74
10	-0.0453	2.999	0.447	1309.75	4.65	0.444	0.995	7.68
11	-0.0460	1.820	0.450	1278.50	4.22	0.440	0.993	9.00
12	-0.0581	1.450	0.414	1127.34	3.17	0.430	0.993	7.89
13	-0.0454	1.473	0.415	1172.66	3.49	0.430	0.995	8.40
14	-0.0731	4.617	0.442	1167.11	2.99	0.448	0.983	7.14
15	-0.0574	3.314	0.429	1156.29	3.54	0.449	0.995	8.52
16	-0.0588	1.577	0.404	1135.03	4.30	0.456	0.992	7.96
17	-0.0544	1.313	0.443	1142.56	4.76	0.467	0.992	9.10
18	-0.0574	1.601	0.531	1144.87	3.98	0.469	0.988	8.30
19	-0.0498	2.488	0.449	1166.24	4.04	0.469	0.992	8.40
20	-0.0615	3.542	0.463	1129.02	4.68	0.454	0.993	7.21
21	-0.0614	2.373	0.400	1144.87	4.44	0.455	0.991	8.15
22	-0.0639	3.261	0.476	1096.62	4.44	0.455	0.991	6.94
23	-0.0650	3.394	0.447	1134.89	4.82	0.475	0.992	8.82
24	-0.0593	1.624	0.558	1118.70	4.76	0.464	0.992	6.57
25	-0.0667	3.236	0.381	1240.49	5.98	0.467	0.993	8.70
26	-0.0452	4.366	0.420	1367.77	5.07	0.443	0.962	7.55
27	-0.0280	3.139	0.404	1269.50	5.14	0.437	0.954	7.51
28	-0.0282	3.868	0.419	1271.94	5.50	0.413	0.954	6.46
29	-0.0206	2.378	0.445	1240.18	3.13	0.430	0.959	7.07
30	-0.0206	3.141	0.408	1241.59	4.38	0.406	0.957	5.00
31	-0.0315	3.725	0.420	1164.80	4.64	0.401	0.955	5.00
32	-0.0491	1.516	0.448	1175.01	3.49	0.427	0.995	8.15
33	-0.0441	3.749	0.383	1224.74	3.96	0.426	0.995	8.30
34	-0.0455	1.618	0.457	1279.61	4.36	0.431	0.994	7.96
35	-0.0488	1.504	0.430	1221.79	3.89	0.427	0.995	8.00
Test set								
36	-0.0479	1.737	0.448	1116.11	3.03	0.431	0.993	7.85
37	-0.0461	1.333	0.408	1214.93	3.89	0.435	0.995	8.52
38	-0.0515	2.451	0.399	1128.24	3.17	0.430	0.993	8.15
39	-0.0590	1.428	0.430	1332.45	4.71	0.442	0.994	8.22
40	-0.0529	1.803	0.362	1175.84	5.31	0.440	0.969	7.19
41	-0.0836	6.139	0.405	1175.54	2.99	0.442	0.981	7.46
42	-0.0590	2.132	0.426	1153.68	3.54	0.449	0.994	7.89
43	-0.0687	3.537	0.480	1095.96	4.44	0.455	0.991	7.33
44	-0.0735	4.708	0.473	1171.69	5.18	0.460	0.993	7.52
45	-0.0315	3.123	0.404	1162.36	4.28	0.426	0.952	6.59

Table 5 Correlation matrix of the descriptors selected

	E_{LUMO}	μ	C_9	V	Log P	ATS7p	AROM
E_{LUMO}	1.000	0.029	-0.253	0.521	-0.002	-0.611	-0.672
μ		1.000	-0.264	0.126	0.128	-0.058	-0.332
C_9			1.000	-0.292	-0.036	0.300	0.173
V				1.000	0.315	-0.263	-0.433
Log P					1.000	0.371	-0.373
ATS7p						1.000	0.238
AROM							1.000

These two properties show the charge distribution of a molecule and are affected by the presence of hydrophilic interactions, which favor hydrogen bonds and dipole-dipole interactions between the two interacting species [47]. We see such interactions happening between the -COOH group of the ligand and the main residues in the active site of the biological receptor (His323, His449 and Tyr473) [45].

(3). The atomic charge of carbon 9 reflects the influence of the substituent groups attached to it that stabilize the ligand in the active site. This property contributes positively to the model; so, high positive charge of carbon 9 (i.e., negative substituent linked to carbon 9) contributes to the increase of biological activity.

(4). Volume is directly related to spatial conformation. Therefore, 3D interactions and the stabilization of the ligand in the active site depend on the size and form of the substance under study [47]. Volume has the most negative influence to the PLS model obtained. In this case, low values of volume can favor the molecule to achieve hydrophilic cavity and interact with important residues. Our compound dataset has some molecules with low biological activity (such as 4 and 7, Table 1) and this can be explained due to steric hindrances.

(5). Log P has a negative contribution to the model. The lipophilic property (partition coefficient) describes the capability of a compound to cross biological membranes. This descriptor is very important, as it can alter the pharmacokinetic properties of the compounds studied and also indicates hydrophobic interactions.

(6). AROM has a positive contribution to the model and represents similar effects to log P. The aromaticity indices are related to hydrophobic interactions and indicate the presence of aromatic groups (benzene rings and double bonds) in the compounds studied. Hydrophobic interactions are important in stabilizing the ligand in the active site. For example, we observe hydrophobic interactions between Cys285 and Leu469 and the double bonds of a crystallographic ligand (eicosapentaenoic acid) [45].

Table 6 Percentage of accumulated information, SEV, PRESS and validation and calibration coefficients for the PLS model

PCs	% accumulated information	SEV	PRESS	q^2	r^2
1	24.37	0.97	32.93	0.57	0.67
2	46.57	0.87	26.41	0.68	0.83
3	62.36	0.79	21.78	0.75	0.88
4	75.05	0.75	19.76	0.80	0.90
5	78.59	0.77	20.61	0.80	0.90
6	92.80	0.78	21.33	0.80	0.90
7	100.00	0.77	20.91	0.80	0.90

Table 7 Experimental and calculated pEC_{50} values and residues for the compounds in the test set

Compound	Experimental pEC_{50}	Predicted pEC_{50}	Residual
36	7.85	7.31	0.54
37	8.52	8.39	0.13
38	8.15	7.71	0.44
39	8.22	8.44	-0.22
40	7.19	7.81	-0.62
41	7.46	6.94	0.52
42	7.89	8.35	-0.46
43	7.33	6.78	0.55
44	7.52	6.94	0.58
45	6.59	6.55	0.04

Finally, we have decided to perform docking studies using some PPARδ ligands of the data set in order to relate to our QSAR analyses and to understand the possible interactions between the compounds studied and the biological receptor. The main ligand-receptor interactions for two compounds of the data set (the most active (17) and the least active one (30)) and the crystallographic ligand (D32) are displayed in Fig. 5.

First, it is important to highlight that the performance of the docking protocol was based on CScore analysis, implemented in the Surflex program. This option takes into account a consensus of the most common scoring functions (GOLD, ChemScore, DOCK and PMF). So, the compounds 17 and 30 had a total score of 8.57 and 8.07, respectively, indicating the best ranking for the compound 17. From Figs. 5a and b, it is possible to observe that the most active compound (17) has similar behavior to the crystallographic ligand in the binding site. Moreover, the least active compound (30) has the polar head and the linker group located at the same position of the crystallographic ligand, but the hydrophobic tail of the compound 30 fulfills another side of the apolar cavity.

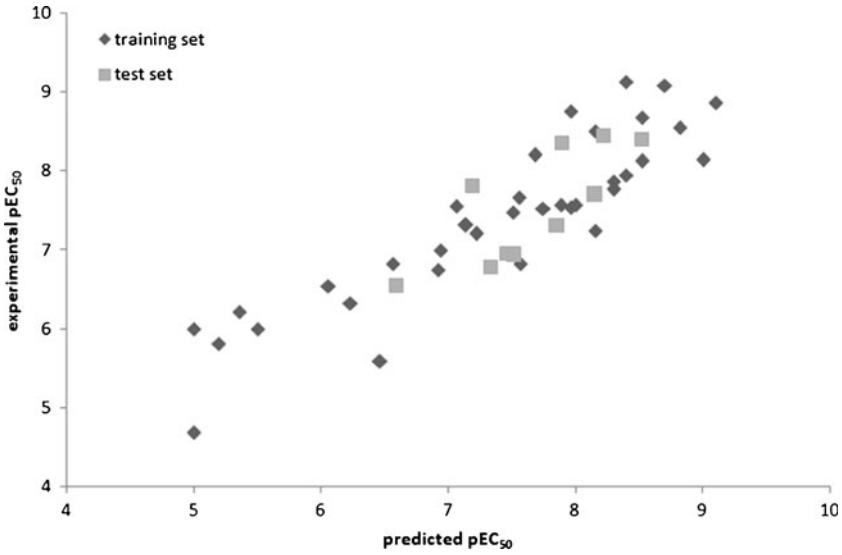


Fig. 4 Experimental versus calculated pEC_{50} values for the compounds studied (training and test sets)

Analyzing the polar interactions (residues in white and blue, Figs. 5c and d) we can note that compound 17 is better directed to polar residues His323, His449 and Tyr473 than compound 30 (the least active). Due to the nature of some electrostatic interactions of the compound 17 with aminoacids of the active site, we can relate them with some electronic properties selected in the multivariate study, such as dipole and ATS7p, which can be considered very important to describe the biological activity presented by the substances studied. Regarding the hydrophobic interactions, it is possible to observe that the hydrophobic tail of compound 17 is located at hydrophobic pocket (colored in orange, Fig. 5b) while the hydrophobic one of compound 30 is not located at the same position, which could disadvantage important interactions with hydrophobic residues in the binding site. An explanation for this could be due to the size of the compound 30, which would cause a stereochemical hindrance and, consequently, decrease the biological activity.

Conclusions

The PPARδ receptor is important in carbohydrate and lipid metabolism, two processes that, when disrupted, lead to *diabetes mellitus* and metabolic syndrome. The main

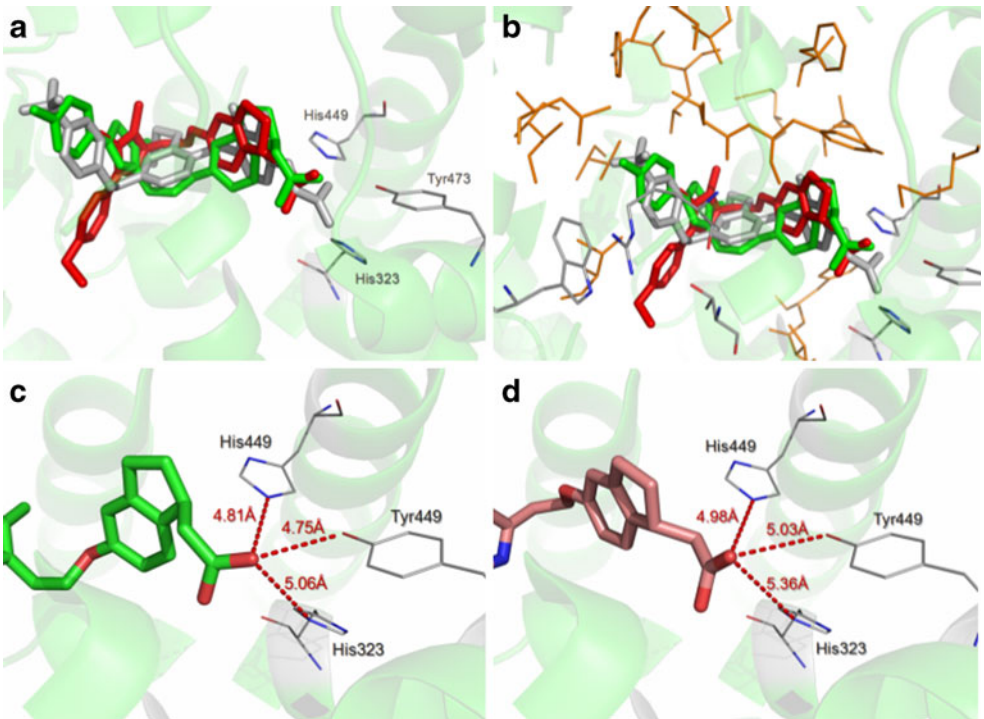


Fig. 5 (**a**) and (**b**) Comparison between docking results and the crystallographic ligand (gray). Docking results for the compounds (**c**) 17 (the most active, colored in green) and (**d**) 30 (the least active, colored in red). Polar residues are colored in white and blue, and hydrophobic ones are orange

objective of this work was to study the quantitative structure-activity relationships of a set containing some PPARδ ligands. We obtained an extended set of electronic, stereochemical, lipophilic and topological properties that were related to biological activity. We used Fisher's weight values and PCA analyses to select the seven most relevant properties for our study: energy of the LUMO, dipole moment, atomic charge at carbon 9, partition coefficient, volume, atomic polarizability and aromaticity index. Using the PLS technique, we constructed a robust statistical multivariate model to predict the biological activity of novel compounds. From the statistical parameters obtained (q^2=0.80 and r^2=0.90), we concluded that our PLS model has good internal consistency. The external validation (compound test set) presented low residual values, indicating that the PLS model is highly reliable. In summary, this study provides insights on the possible effects (electronic, stereochemical, lipophilic and topological) involved in the interaction between the compounds studied and the PPARδ receptor, and these findings should be useful for the design of new structurally related PPARδ ligands having improved biological activity.

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