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Original article

QSAR analysis of PPAR-γ agonists as anti-diabetic agents☆

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Abstract

QSAR studies have been performed on some PPAR-γ agonists using TATA-BioSuite software to identify the essential structural and physicochemical features for their PPAR-γ agonistic activity. The 23 compounds were divided into training set of 18 and test set of five compounds using *k*-nearest neighbor (kNN) clustering. The steric, electronic and topological descriptors were found to have an important role in governing the variation in agonistic activity. The predicted activities by the developed models were in good accordance with the observed activities.

Keywords: QSAR; Diabetes; PPAR-γ agonists; Regression analysis; Thiazolidinediones

1. Introduction

Type 2 diabetes is a debilitating disease characterized by hyperglycemia due to insulin resistance in the liver and peripheral tissues. In US, approximately 16 million people suffer from type 2 diabetes and an additional 14 million have impaired glucose tolerance [1]. Type 2 diabetes is a chronic disease characterized by insulin resistance in the liver and peripheral tissues accompanied by a defect in pancreatic β-cells [2,3]. The insulin resistant state at the peripheral level causes impaired glucose utilization leading to hyperglycemia, which may also play a role in the etiology of a wide spectrum of metabolic disorders such as obesity, hypertension, atherosclerosis, neuropathy, nephropathy, retinopathy, etc. [4,5]. Most commonly employed oral hypoglycemic agents are sulfonylureas and biguanides which have the disadvantage such as primary and secondary failure of efficacy as well as the potential for induction of severe hypoglycemia [6]. Hence there is a need for new candidate molecules which may effectively reduce insulin resistance or potentiate insulin action in genetically diabetic or obese individuals. The search for the drugs that reverse the insulin resistance without stimulating insulin release from β-cells also fulfills a major medical need in the treatment of NIDDM. Hence the search for such drugs with a potential to reduce long term complications of NIDDM, is of current interest. Between 1997 and 1999, a new class of drugs called 'glitazones' [7] was approved by the FDA for the treatment of type 2 diabetes. These agents share a common partial chemical structure: thiazolidine-2,4-dione (TZD). Glitazones correct hyperglycemia by enhancing tissues' sensitivity to insulin. Because of this mechanism of action, glitazone treatment is not associated with dangerous hypoglycemic incidents that have been observed with conventional sulfonylurea agents and insulin therapy. In the mid-1990s, the molecular target of glitazones was reported to be the peroxisome proliferator-activated receptor-γ (PPAR-γ) [8–11]. The PPARs are a group of nuclear receptors that act as transcriptional factors which play a major role in the regulation of lipid metabolism and storage. The TZDs are found to be the promising compounds capable of ameliorating NIDDM by improving insulin resistance without inducing hypoglycemia [12]. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue, resulting in the correction of elevated plasma level of glucose without the occurrence of hypoglycemia. But undesirable effects associated with glitazones have been observed in

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Table 1
The structures and observed activities of the compounds

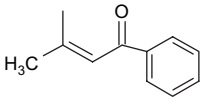
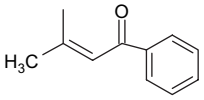
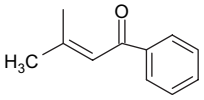
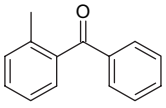
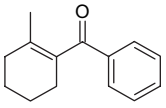
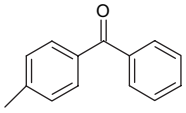
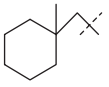
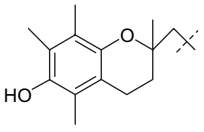
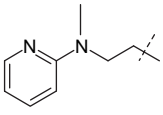
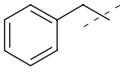
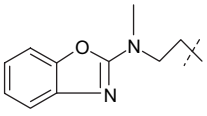
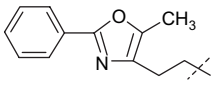
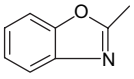
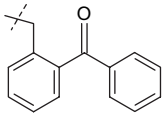
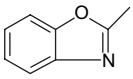
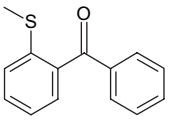
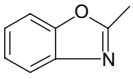
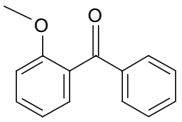
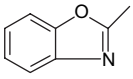
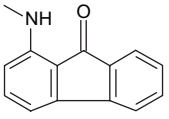
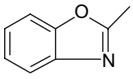
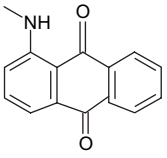
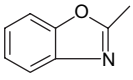
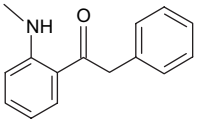
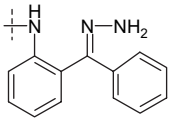
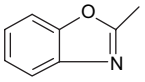
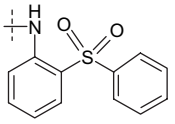
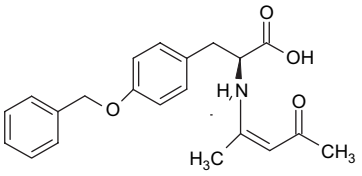
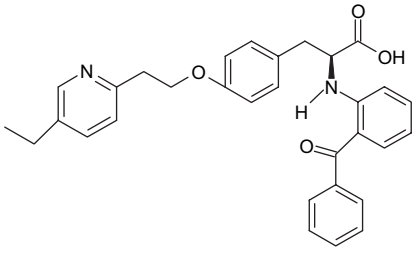
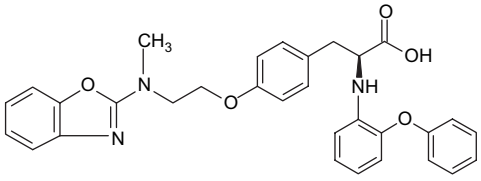
Comp.	Substituents		Obs. act. (log pki)
	X	R	
1	OH		0.899
2	NH_2		0.769
3	OCH_3		0.786
4	OH		0.785
5	OH		0.831
6[a]	OH		0.770
7			0.862
8[a]			0.918
9			0.946
10			0.847
11			0.95
12			0.951
13			0.877

Table 1 (*continued*)

Comp.	Substituents		Obs. act. (log pki)
	X	R	
14			0.879
15			0.874
16[a]			0.849
17			0.918
18			0.928
19			0.839
20			0.831
21			0.756
22[a]			0.913

(*continued on next page*)

Table 1 (*continued*)

Comp.	Substituents		Obs. act. (log pki)
	X	R	
23[a]			0.925

Refer Figs. 1–3.
[a] Test set molecules.

animal and human studies, which include cardiac hypertrophy, haemodilution and severe liver toxicity. Therefore efforts are being put in to develop molecules which are devoid of such toxicity. However, it still remains unclear whether the side effects are caused by the mechanism of action of these compounds, or originate within the TZD chemical structure which is common to this class. Therefore the emphasis is on the development of non-thiazolidinedione PPAR-γ agonists, which might surmount the problem, associated with the known TZDs and thus may offer an advantage as an anti-diabetic agent.

In view of above, there is a need for the development of 3D-QSAR models and identification of pharmacophore in terms of essential structural and electronic features important for the PPAR-γ agonistic activity. Though some 3D-QSAR studies of TZDs have been reported, however, no such studies have been carried out on non-TZDs. Our previous work of the 3D-QSAR study based on logico-structural based approach (Apex-3-D) has been done on these non-TZDs [13]. A different and simple approach has been applied in *N*-(2-benzoyl phenyl)-L-tyrosines PPAR-γ agonists in order to evaluate the performance of TATA BioSuite 1.0 software and to achieve quality models for PPAR-γ agonistic activity and the results are described in this paper.

2. Materials and methods

The biological activity data were taken from Henke et al. [14]. The biological activity is given in the form of PPAR-γ agonistic activity (log pki) (Table 1).

2.1. Computational approach

SYBYL6.9 [15] was used for sketching molecular structures and TATA BioSuite 1.0 [16] software was used for calculation of various physico-chemical parameters. The selection of training and test set is very important in QSAR studies. TATA BioSuite has various inbuilt functions for this, such as *k*-means clustering, *k*-nearest neighbor (kNN) and others. We used kNN [17] clustering for the selection of test set. In kNN clustering molecules were grouped on the basis of similarity in terms of calculated physico-chemical parameters with other compounds in the data set.

In kNN a distance is assigned between all points in a dataset. This distance is defined as the Euclidean distance between two points. It can be represented as:

$$d = \sqrt{\sum_{i=0}^{i=n} (x_i - y_i)^2}$$

From these distances, a distance matrix is constructed between all possible pairings of points (x, y). Each data point within the data set has a class label in the set, $C = \{c1,\ldots,cn\}$. The data points', *k*-closest neighbors (*k* being the number of neighbors) are then found by analyzing the distance matrix. The *k*-closest data points are then analyzed to determine class label which is the most common among the set. The most common class label is then assigned to the data point being analyzed. Five groups were made according to kNN clustering and one compound was chosen from each cluster for the test set so as to represent full parameter space in both the sets, the rest of the compounds were put in training set.

Table 2
Correlation matrix for the parameters used

	ACT	MR	HBA	Jurs_WNSA3	Jurs_RNCG	Jurs_RNCS	HF	DIP-X	Jurs_TASA	DIP-Z	DIP-Y
ACT	1.00										
MR	0.73	1.00									
HA	0.61	0.74	1.00								
Jurs_WNSA3	−0.51	−0.70	−0.74	1.00							
Jurs_RNCG	−0.60	−0.52	−0.29	−0.04	1.00						
Jurs_RNCS	0.55	0.38	0.14	−0.06	−0.53	1.00					
HF	0.20	0.41	0.00	0.01	−0.24	0.25	1.00				
DIP-X	−0.08	0.30	0.37	−0.45	0.06	0.17	−0.21	1.00			
Jurs_TASA	0.74	0.97	0.80	−0.70	−0.54	0.41	0.33	0.35	1.00		
DIP-Z	0.50	0.45	0.33	−0.60	−0.04	0.43	−0.01	0.32	0.47	1.00	
DIP-Y	−0.39	−0.61	−0.57	0.56	0.29	−0.58	0.05	−0.60	−0.69	−0.60	1.00

Table 3
Observed activity and calculated physico-chemical parameters of the compounds

Comp.	Activity	HF	DIP-X	DIP-Y	DIP-Z	Jurs_TASA	Jurs_RNCG	Jurs_RNCS	MR	HBA	Jurs_WNSA3
1	0.89	−64.37	−1.83	1.45	0.95	645.15	0.09	340.67	120.27	5	−24.81
2	0.77	−15.68	0.69	2.43	1	660.64	0.1	46.34	121.83	4	−29.37
3	0.79	−47.19	−1.09	1.4	0.28	666.6	0.09	138.11	124.65	5	−34.88
4	0.79	−79.36	1.58	2.47	−1.94	707.56	0.08	0	132.01	5	−33.14
5	0.83	−44.2	−2.63	2.02	3.24	701.19	0.09	12.7	132.55	5	−36.74
7	0.86	−99.1	−2.18	1.49	1.6	720.57	0.08	82.82	138.2	5	−35.53
9	0.95	−20.12	−3.16	2.55	2.45	793.77	0.08	134.29	144.51	6	−48.47
10	0.85	−44.73	−2.18	1.36	1.7	722.6	0.09	64.1	132.55	5	−31.51
11	0.95	−20.58	−0.26	1.88	4.29	846.71	0.07	284.31	153.8	6	−43.27
12	0.95	−41.6	−2.51	1.01	0.45	897.94	0.08	102.36	158.39	7	−52.42
13	0.88	−9.13	0.13	−0.42	1.68	882.37	0.07	183.04	153.58	6	−41.7
14	0.88	−23.63	2.26	−1.06	2.46	846.69	0.07	390.06	156.03	6	−38.29
15	0.87	−60.57	1.18	−1.56	3.04	887.12	0.07	232.97	150.8	7	−38.94
17	0.92	−86.76	2.29	−0.21	1.91	866.44	0.07	70.09	154.24	8	−56.87
18	0.93	−29.11	0.77	−2.14	4.68	890.79	0.07	415.25	158.4	6	−57.87
19	0.84	49.67	−3.18	2.77	−1.87	789.95	0.08	85.51	150.91	6	−30.08
20	0.83	−57.12	3.03	−0.31	4.24	821.87	0.12	8.51	151.64	7	−71.77
21	0.76	−101.1	−1.55	2.82	−0.31	578.3	0.1	15.9	100.18	5	−24.47
6[a]	0.77	−31.7	−0.91	−1.72	2.09	716.89	0.08	163.18	132.55	4	−37.79
8[a]	0.92	−148.36	−2.58	1.3	2.4	865.04	0.07	32.78	166.68	7	−32.27
16[a]	0.85	−13.74	−1.88	0.12	2.86	907.85	0.07	30.88	153.68	6	−40.33
22[a]	0.91	−55.33	−2.55	1.42	−0.26	798.98	0.08	322.89	144.32	6	−46.49
23[a]	0.93	−19.83	0.58	1.01	2.11	870.75	0.07	54.41	150.44	6	−45.92

[a] Molecules of test set.

3. Result and discussion

BioSuite calculates a large number of physico-chemical parameters (90 in total) covering different classes like thermodynamic, topological, structural, electronic and geometrical. The use of all of them in one MLR analysis is not possible as the data set has only 23 compounds, therefore the parameters were taken class-wise first for the development of QSAR equations. Then the significant parameters from different classes were grouped together to get other regression models.

Table 4
The predicted and residual activities obtained from different equations

Comp.	Act.	EEq1	REq1	EEq2	REq2	EEq3	REq3	EEq4	REq4	EEq5	REq5
1	0.89	0.805	0.085	0.83	0.059	0.85	0.043	0.8	0.09	0.83	0.065
2	0.77	0.758	0.011	0.81	−0.037	0.81	−0.037	0.79	−0.024	0.78	−0.013
3	0.79	0.8	−0.014	0.83	−0.04	0.82	−0.032	0.83	−0.047	0.83	−0.044
4	0.79	0.799	−0.014	0.79	−0.006	0.83	−0.042	0.85	−0.06	0.84	−0.057
5	0.83	0.842	−0.011	0.89	−0.06	0.82	0.007	0.84	−0.005	0.83	0.002
7	0.86	0.869	−0.007	0.88	−0.018	0.85	0.014	0.85	0.009	0.84	0.018
9	0.95	0.895	0.051	0.94	0.009	0.89	0.055	0.9	0.051	0.88	0.066
10	0.85	0.848	−0.001	0.88	−0.035	0.83	0.021	0.83	0.022	0.83	0.016
11	0.95	0.886	0.064	0.94	0.008	0.94	0.012	0.9	0.048	0.89	0.055
12	0.95	0.957	−0.006	0.96	−0.011	0.9	0.048	0.91	0.041	0.91	0.039
13	0.88	0.897	−0.02	0.93	−0.054	0.89	−0.009	0.89	−0.014	0.89	−0.012
14	0.88	0.851	0.028	0.89	−0.013	0.93	−0.047	0.89	−0.012	0.9	−0.017
15	0.87	0.905	−0.031	0.93	−0.057	0.87	0.002	0.89	−0.013	0.92	−0.047
17	0.92	0.887	0.031	0.9	0.022	0.87	0.05	0.94	−0.024	0.96	−0.039
18	0.93	0.901	0.027	0.95	−0.026	0.92	0.005	0.94	−0.014	0.9	0.031
19	0.84	0.866	−0.027	0.9	−0.057	0.9	−0.064	0.85	−0.007	0.88	−0.039
20	0.83	0.838	−0.007	0.89	−0.054	0.85	−0.016	0.83	0.003	0.81	0.018
21	0.76	0.775	−0.019	0.78	−0.027	0.74	0.014	0.77	−0.011	0.8	−0.045
6[a]	0.77	0.821	−0.051	0.87	−0.095	0.8	−0.033	0.86	−0.085	0.81	−0.042
8[a]	0.92	0.981	−0.063	0.96	−0.046	0.92	0	0.88	0.038	0.93	−0.011
16[a]	0.85	0.943	−0.094	0.98	−0.132	0.86	−0.014	0.89	−0.04	0.89	−0.042
22[a]	0.91	0.904	0.009	0.91	0.006	0.91	0.001	0.88	0.028	0.88	0.037
23[a]	0.93	0.888	0.037	0.92	0.002	0.87	0.054	0.9	0.025	0.89	0.037
Pred. r^2	*0.41*		*0.22*		*0.80*		*0.65*		*0.67*		

EEq is the estimated activity from the respective equation; REq is the residual from the respective equation; Pred. r^2 is predictive r^2 calculated using test set compounds.

[a] Molecules of test set.

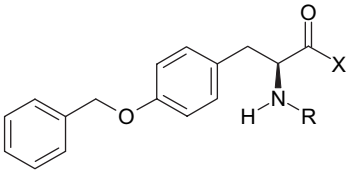


Fig. 1. Compounds **1**–**6**.

The thermodynamic, electronic and structural parameters were found to be dominating in explaining the variation in activity as evidenced by the following QSAR equations.

$$-\log EC_{50} = 0.3656(\pm 0.0890) - 0.0004(\pm 0.0002)\text{HF} - 0.0144(\pm 0.0004)\text{DIP-X} + 0.0006(\pm 0.0001)\text{Jurs\_TASA}$$
$$N = 18,\ q^2 = 0.530,\ r^2 = 0.718,\ r = 0.848,\ s = 0.036,\ F\text{-test} = 11.908 \quad (1)$$

$$-\log EC_{50} = 0.4758(\pm 0.0752) - 0.0133(\pm 0.0045)\text{DIP-X} + 0.0091(\pm 0.0051)\text{DIP-Z} + 0.0005(\pm 0.0001)\text{Jurs\_TASA}$$
$$N = 18,\ q^2 = 0.551,\ r^2 = 0.737,\ r = 0.858,\ s = 0.035,\ F\text{-test} = 13.065 \quad (2)$$

$$-\log EC_{50} = 0.4098(\pm 0.108) + 0.0137(\pm 0.009) \times \text{DIP-Y} + 0.0002(\pm 0.0000) \times \text{Jurs\_RNCS} + 0.0029(\pm 0.0007) \times \text{MR}$$
$$N = 18,\ q^2 = 0.442,\ r^2 = 0.676,\ r = 0.823,\ s = 0.039,\ F\text{-test} = 9.762 \quad (3)$$

$$-\log EC_{50} = 0.9879(\pm 0.0642) - 0.0026(\pm 0.0007) \times \text{Jurs\_WNSA3} - 2.7977(\pm 0.6845) \times \text{Jurs\_RNCG}$$
$$N = 18,\ q^2 = 0.462,\ r^2 = 0.649,\ r = 0.806,\ s = 0.039,\ F\text{-test} = 13.906 \quad (4)$$

$$-\log EC_{50} = 0.8659(\pm 0.1041) + 0.0295(\pm 0.0109) \times \text{HBA} - 2.0895(\pm 0.7906)\text{Jurs\_RNCG}$$
$$N = 18,\ q^2 = 0.401,\ r^2 = 0.570,\ r = 0.755,\ s = 0.043,\ F\text{-test} = 9.937 \quad (5)$$

Here N is number of compounds, q^2 is leave one out cross-validated r^2, r^2 is coefficient of determination, r is correlation coefficient, s is standard error and F-test is F-value for Fischer's test of significance. It can be seen that all equations are statistically highly significant as evidenced by statistical parameters. The equations contain DIP-X, DIP-Y, DIP-Z, MR, HF and various Jurs descriptors. The dipole moment (DIP) descriptor is a 3D electronic descriptor that indicates the strength and orientation behavior of a molecule in an electrostatic field. The molar refractivity (MR) is the molar volume corrected by the refractive index. It represents size and polarizability of a fragment or molecule. Molar refractivity is given by:

$$\text{MR} = \left(\frac{(n^2-1)}{(n^2+2)}\right)\frac{(\text{MW})}{d}$$

where n is the refractive index, MW is the molecular weight, and d is the compound density. Heat of formation (H_f) represents the chemical stability and reactivity of the molecules. The studies show a negative correlation between heat of formation and activity, that is, more negative the heat of formation value means more thermodynamically stable is the molecule and higher is the PPAR-γ agonist activity. Jurs_RNCS is calculated as relative negative charge surface area mapped over the solvent-accessible surface area of individual atoms, Jurs_TASA is calculated as total hydrophobic surface area while Jurs_RNCG is relative negative charge i.e. most negative charge/total negative charge. These surface area descriptors are important as they may indicate the factors influencing the binding of a ligand to its target.

It can be seen from the correlation matrix (Table 2) that the parameters used in the equations are fairly independent (intercorrelation < 0.61). The observed activity and various physicochemical parameters which were used in the development of these equations are given in Table 3. The predicted and residual activities for different equations are given in Table 4.

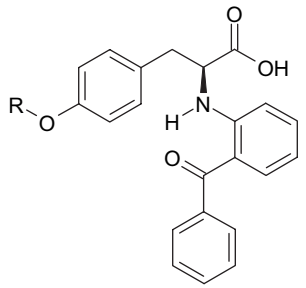


Fig. 2. Compounds **7**–**12**.

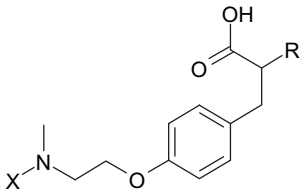


Fig. 3. Compounds **13**–**21**.

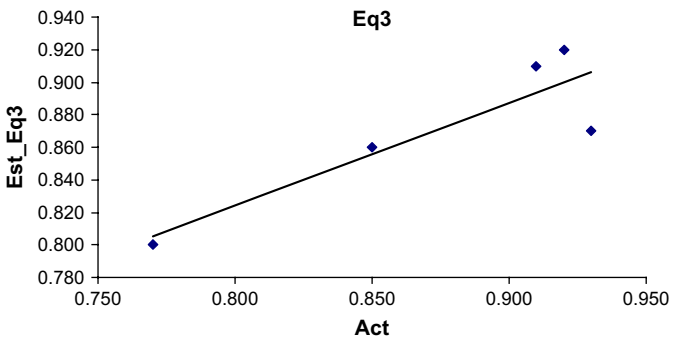


Fig. 4. The plot between observed and predicted activities from Eq. (3).

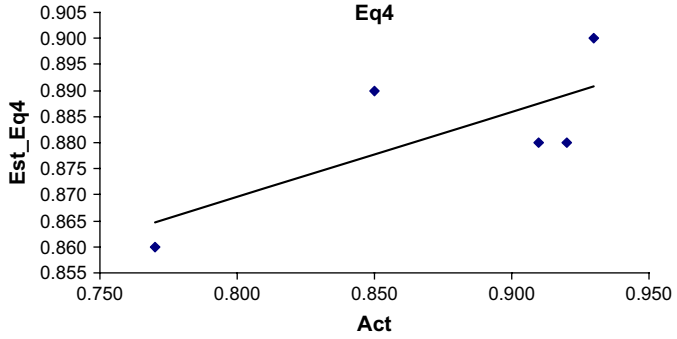


Fig. 5. The plot between observed and predicted activities from Eq. (4).

3.1. Validation by external test set

In QSAR modelling, it is very important to validate the relevance of the resulting model. The most important validation is external validation, which consists of making predictions for an independent set of compounds not used in the model training. The predictivity of generated QSAR equations was tested using the test set consisting of five compounds selected earlier. A good correlation was found between the observed and the predicted activities of Eqs. (3)–(5) as evident by their predictive r^2 (r^2 between observed and predicted activities) which is more than 0.65 (Table 4).

Among the five generated equations Eq. (1) has high r^2 (0.718) and q^2 (0.53) values but has moderate pred. r^2 value (0.441) for the test set prediction. This may be explained in view of the recent observation that q^2 may be a necessary but not sufficient condition for good predictivity [18] and hence an importance is given for external test set prediction. Eq. (2) has the highest r^2 (0.738) and q^2 (0.551) values but has less pred. r^2 value (0.22) for the test set and hence cannot be considered as a reliable model. Eq. (3) has good r^2 (0.676) and moderate q^2 (0.441) values but with unusually higher pred. r^2 (0.80) than r^2. Moreover the independent parameter DIP-Y used in this equation has some intercorrelation with MR (−0.61) and Jurs_RNCS (−0.58) (Table 2, Fig. 4), therefore even this equation with good external predictivity may not be considered better than Eq. (4) which contains only two parameters with negligible intercorrelation (<0.04), a reasonable q^2 (0.462) value, with similar r^2 of the training (0.649) and test (pred. $r^2 = 0.65$) sets and the highest F-value (13.906) among all generated equations (Fig. 5). Eq. (5) is statistically poorer and also has low q^2 (0.401) and r^2 (0.57) values (Fig. 6), therefore Eq. (4) may be considered as the most useful QSAR model.

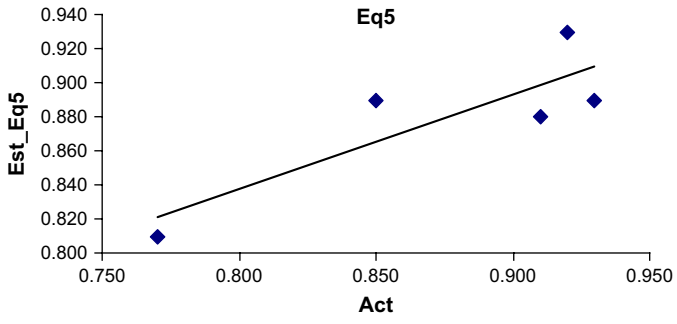


Fig. 6. The plot between observed and predicted activities from Eq. (5).

The most important parameter seems to be the Jurs_RNCG (relative negative charge = most negative charge/total negative charge) as it has the highest contribution in Eq. (4) but the contribution of other parameters viz. MR, Jurs_TASA and HBA showing high correlation 0.73, 0.74 and 0.61, respectively (Table 2), with biological activity cannot be ruled out. Therefore these four parameters may be considered important for designing the new molecules. The positive coefficient with MR, Jurs_TASA and HBA in Eqs. (2), (3) and (5), respectively, and negative coefficient with Jurs_RNCG parameter indicate that the new molecules with high steric bulk, hydrophobicity, increased number of hydrogen bond acceptor atoms and higher total negative charge (to reduce the value of Jurs_RNCG) should lead to the molecules with higher activity.

4. Conclusion

The 2D-QSAR studies were done on a series of PPAR-γ agonists and some useful relationships were found. The steric, electronic and topological descriptors were found to have important role in governing the variation in PPAR-γ agonistic activity. An important observation was made that QSAR study based on linear free energy approach is sufficient to generate high quality predictive models. The current model is a good improvement over the previous models [13]. As the generated models predicted well the observed variance in the activity in both the training and the test sets, these models are useful for further optimization of the activities in this series of compounds.

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