Interdiscip Sci Comput Life Sci (2015) 7: 335–346
DOI: 10.1007/s12539-015-0009-y

Prospective QSAR-based Prediction Models with Pharmacophore Studies of Oxadiazole-substituted α-isopropoxy Phenylpropanoic Acids on with Dual Activators of PPARα and PPARγ

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Received 14 October 2013 / Revised 22 November 2013 / Accepted 5 December 2013

Abstract: A series of oxadiazole-substituted α-isopropoxy phenylpropanoic acids with dual activators of PPARα and PPARγ derivatives were subjected to two dimensional and *k-nearest neighbour* Molecular field analysis. The statistically significant best 2D-QSAR (PPARα) model having good predictive ability with statistical values of $r^2 = 0.8725$, $q^2 = 0.7957$ and pred_$r^2 = 0.8136$, was developed by GA-PLS with the descriptors like SsClcount, SddsN (nitro) count and SsOHcount contribute significantly to the biological activity. The best 3D-QSAR studies (PPARα) were performed using the genetic algorithm selection k-nearest neighbor molecular field analysis approach; a leave-one-out cross-validated correlation coefficient q^2=0.7188 and predicate activity pred_r^2 =0.7508 were obtained. The influences of steric and electrostatic field effects generated by the contribution plots are discussed. The best pharmacophore model includes three features *viz.* hydrogen bond donor, hydrogen bond acceptor, and aromatic features were developed. The information rendered by 2D, 3D QSAR models may lead to a better understanding of structural requirements of substituted α-isopropoxy phenylpropanoic derivatives and also aid in designing novel potent PPARα and PPARγ for antihyperglycemic molecules.
Key words: phenylpropanoic, PPARα, PPARγ, 2D QSAR, *k-nearest neighbor*, pharmacophore, antihyperglycemic, VLife MDS.

1 Introduction

Type 2 diabetes is a debilitating disease characterized byhyperglycemia due to insulin resistance (IR) in the liverand peripheral tissues. In the US, approximately 16 million people suffer from type 2 diabetes and an additional 14 million have impaired glucose tolerance (Smith *et al.*, 2000). Type 2 diabetes is a metabolic disorder that affects approximately150 million people worldwide with projections of 300 millionpeople by the year 2025 (WHO, 2002; Jönsson *et al.*, 2002). The PPARs (peroxisome proliferator activated receptors) were cloned less than a decadeago and are members of the super family of nuclear transcription factors that includes thereceptors for steroid, retinoid, and thyroid hormones (Mangelsdorf and Evans, 1995). Coronary heart disease (CHD) remains the leading cause of death in the developed world and is linked to a number of associated risk factors including hypertriglyceridemia and hypercholesterolemia. As members of the nuclear hormone receptor super family of ligand-activated transcription factors, the peroxisome proliferator-activated receptors (PPARs) regulate a multitude of cellular processes including the storage and catabolism of dietary fats and carbohydrates (Lemberger *et al.*, 1996). PPARs, which belong to a nuclear hormone receptor super family, act as transcription factors in the regulation of genes involvedin glucose and lipid homeostasis (Shearer and Billin, 2007). Up to date, three PPAR subtypes, PPARα, PPARγ and PPARδ have been identified. Activation of PPAR$\alpha$by fibrates, such as fenofibrate, is known to be useful in thetreatment of dyslipidemia. On the other hand, compounds thatact on both PPARα and γ including ragaglitazar, muraglitazarand tesaglitazar have been identified as very attractive candidatesin the treatment of dyslipidemic type 2 diabetes (Staels and Fruchart, 2005; Gross *et al.*, 2007; Willson *et al.*, 2000). These receptors are important regulators in multiple physiological pathways, such as glucose homeostasis, fatty acid metabolism, inflammation, and cellular differentiation (Kersten *et al.*, 2000). Glitazones and fibrates are two classes of PPAR drugs currently being marketed for the treatments of insulin resistance and dyslipidemia, respectively. Glitazones

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(pioglitazone and rosiglitazone) are insulin sensitizers functioning through PPAR γ activation (Berger *et al.*, 1996). 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 γ agonists enhance insulin action and promote glucose utilization in peripheral tissues. PPARα agonists improve insulin sensitivity associated with obesity and mediate their effects on lipid metabolism. Therefore PPARα/ γ dual activators provide superior profile toward the control of hyperglycemia and hypertriglyceridemia. PPARγ is mainly expressed in insulin sensitive tissues such as adipocytesand to a lesser extent in muscle and liver. It ishypothesized that their activation by TZDs affect theexpression of a number of genes involved in lipid andglucose metabolism and preadipocyte differentiation (Spiegelman, 1998; Brun *et al.*, 1997), Both rosiglitazone and pioglitazone are potentagonists of PPARγ. Designing compounds with PPARα activity in addition to PPARγ agonist activity may offer improved alternatives toward control of hyperglycemia and hypertriglyceridemia in type 2 diabetics (Murakami *et al.*, 1998). Many synthetic dual PPARα/γ agonists have been developed to treat type 2 diabetes (T2D) and metabolic syndrome and have been shown to be beneficial as compared with selective PPARR or PPARγ agonists because they improve lipid and glucose homeostasis (Sauerberg *et al.*, 2002). However, the adverse toxicity profiles of dual PPARα/γ activators have raised critical safety issues, which have caused developmental programs to be discontinued (Nissen *et al.*, 2005). Studies also show that PPARγ is the receptor for a well-known class of antidiabetic drugs, thiazolidinedione (Lehmann *et al.*, 1995). Thiazolidinedione derivatives (glitazones) (Sohda *et al.*, 1982; Oberfield *et al.*, 1999) and other classes of insulin sensitizers such as oxazolidinediones (Dow *et al.*, 1991; Momose *et al.*, 2002), isoxazolidinediones (Shinkai *et al.*, 1998) tetrazoles and tyrosine derivatives (Collins *et al.*, 1998) are found to specifically sensitize PPARγ. The fibrate class of antilipidemic agents act as agonists for PPARα. Propionic acid derivatives (ragaglitazar) have been found to be dual activators for PPARR and PPARγ (Buckle *et al.*, 1996; Henke, 2004; Lohray *et al.*, 1999). PPARδ is expressed in most cell types; several studies indicate that PPARδ agonists play important roles in dyslipidemia (Oliver *et al.*, 2001), cancer treatment (Park *et al.*, 2001) and differentiation of cells within the central nervous system (Basu-Modak *et al.*, 1999). Interestingly, a recent report shows that PPARδ agonists could stimulate muscle fiber transformation and enhance physical endurance (Wang *et al.*, 2004). Current drugs used for the treatmentof type 2 diabetes are selected from biguanides, sulfonylureas, insulin formulations, glinides, a-glucosidase inhibitors (Wagman and Nuss, 2001), dipeptidyl peptidase IV inhibitors (Kim *et al.*, 2005), Glucagon-like peptide (GLP)-1 analogs (Joy *et al.*, 2005) and peroxisome proliferator activated receptor (PPAR) δ agonists. Although treatment with highly active thiazolidinedione (TZD) class of drugs has significantlyimproved the clinical situation, suffers with adverse sideeffects of hepatotoxicity, weight gain and edema (Ram, 2003; Diamant and Heine, 2003). In addition to the characteristiccombination of insulin resistance and insulin deficiency, the type 2 diabetic often displayscardiovascular risk factors including dyslipidemia (hypertriglyceridemia, low HDL, andsmall dense LDL), hypertension, and obesity (Amos *et al.*, 1997). Quantitative structure activity relationship (QSAR) which has become a popular tool for establishing quantitative relationship between biological activity and descriptors representing physicochemical properties of the compounds in aseries using statistical methods and it helps topredict the biological activities of newly designed analogues contributing to the drug discovery processes (Ferreira, 2002). The prime feature of QSAR is to establish a correlation between various molecular properties of a set of molecules with their experimentally known biological activity. 2D-QSAR relationship is a rough approximation and contains topological or two-dimensional (2D) information. It explains how the atoms are bonded in a molecule, the type of bonding, and the interaction of particular atoms (e.g., total path count, molecular connectivity indices, etc.). Pharmacophore modeling correlates activities with the spatial arrangement of various chemicalfeatures (Sotriffer *et al.*, 1996).

In the search of new oxadiazole-substituted α-isopropoxy phenylpropanoic acids entities with improved PPARα and PPARγ activity, this study deals with 2D-QSAR, 3DQSAR, and pharmacophore approaches using V-Life Science Version 3.5 molecular design software to find out structure features required for biological activity. These identified important structural features could subsequently be utilized to design novel potent dual activators on PPARα and PPARγ.

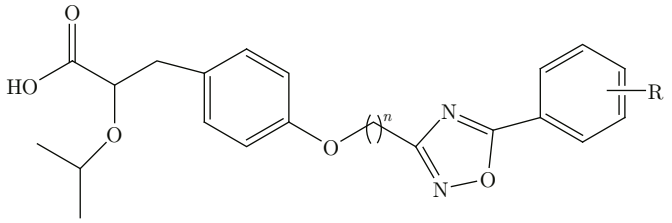
2 Materials and method

All computational workwas performed on a HP Compaq PC running on Intel Pentium-D processor. The molecular structures of the compounds in the data set were sketched using V-life MDS (Molecular Design Suite) TM$^{3.5}$ software supplied by V-life Sciences Technologies Pvt. Ltd., Pune, India.

2.1 Data set of Biological Activities

A series of 26 analogues of oxadiazole-substituted α-isopropoxy phenylpropanoic acids with dual agonist PPARα and PPARγ activity on were selected and activity data (EC_{50}nm) were collected from published literature (Liu *et al.*, 2001). The biological activities

Table 1 Structure and activity of oxadiazole substituted α-isopropoxy phenylpropionic derivatives



Com.No	n	R	IC_{50} (PPARα)	pIC_{50} (PPARα)	IC_{50} (PPARγ)	pIC_{50} (PPARγ)
1	1	H	160	2.204	79	1.897
2	1	3-F	79	1.897	100	2.000
3	1	4-F	160	2.204	200	2.301
4*	1	2-CH_3	40	1.602	100	2.000
5	1	3-CH_3	79	1.897	50	1.698
6*	1	4-CH_3	25	1.397	16	1.204
7	1	4-Cl	13	1.113	20	1.301
8	1	4-Br	40	1.602	32	1.505
9	1	4-CF_3	32	1.505	25	1.397
10*	1	4-CF_3O	20	1.301	63	1.799
11	1	4-$CH(CH_3)_2$	13	1.113	4	0.602
12	1	4-$C(CH_3)_3$	40	1.602	3	0.477
13	1	3,5-di-F	40	1.602	100	2.000
14*	1	3,5-di-CF_3	6	0.778	32	1.505
15	1	C_6H_{11}	240	2.380	230	2.361
16	2	H	2000	3.301	13	1.113
17	2	3-F	500	2.698	2	0.301
18	2	4-F	790	2.897	40	1.602
19*	2	4-Cl	400	2.602	25	1.397
20	2	3-Cl	320	2.505	4	0.602
21	2	3-CF_3	200	2.301	6	0.778
22	2	2-CF_3	400	2.602	160	2.204
23*	2	3,5-di-CF_3	50	1.698	4	0.602
24	—	3,5-di-CF_3	6	0.778	32	1.505
25	—	3,5-di-CF_3	4	0.602	32	1.505
26	—	3,5-di-CF_3	2500	3.397	630	2.799

*Test Compound

were converted into the corresponding pIC_{50} values (-log EC_{50}), where IC_{50} value represents the drug in molar concentration that causes 50% of inhibition. Our aim is to utilize these activity data for the development of a valid QSAR models based on 2D and 3D-QSAR model based on steric and electrostatic fields that gives a deep insight into structure- property-activity correlations. The compounds along with their inhibitory data (as reported in literature and also in its negative logarithmic form) are presented in Table 1. The dataset of 26 molecules was divided into training and test set by sphere exclusion method (Golbraikh and Tropsha, 2002) for PLS model with pIC_{50} activity field as dependent variable and various 2D descriptors calculated for the molecules as independent variables. Six compounds namely **4, 6, 10, 14, 19**, and **23**, were used as test set, while the remaining molecules were used as the training set.

2.2 Molecular modeling

The sketched structures were used for the calculation of 2D molecular descriptors using QSAR module of Molecular design suite software. All the compounds werebatch optimized for the minimization of energies and optimization of geometry using Merck molecular force field, followed by considering distance-dependent dielectric constant of 1.0, convergence criterion or root mean square (RMS) gradient at 0.01 kcal/mol Å (Halgren, 1996) and the iteration limit to 10 000. Selection of the training andthe test set for the QSAR model was done byconsidering the fact that the test set compounds should represent structural diversity and a range of bi-

Table 2 Selected descriptors parameters of phenylpropionic derivatives (PPARα and PPARγ)

SsCl count	SsOH count	$SsCH_3$ Count	T_1_Cl_1	E_802	E_99	S_747	S_264
0	6.246628	2.975211	1	−0.63170	−0.91868	−0.18933	−0.39496
0	8.138522	2.979642	0	−0.33751	−0.50552	−0.26150	−0.03465
0	7.042682	3.241557	0	−0.33484	−0.68175	−0.17598	−0.35290
1	6.217063	3.333259	2	−0.42184	−0.61580	−0.26706	−0.45463
3	7.578866	3.277148	6	−0.14307	−0.50179	−0.22729	−0.41420
0	6.793475	3.433304	0	−0.48077	−0.95821	−0.16848	−0.30252
0	6.432420	2.939990	0	−0.58467	−1.02430	−0.24162	−0.43852
0	6.542894	3.081704	0	−0.63440	−0.94613	−0.19002	−0.40024
1	5.991743	3.025575	1	−0.51682	−0.69920	−0.18227	−0.38014
1	6.246628	2.187287	1	−0.46008	−0.84799	−0.27950	−0.49602
0	6.432420	2.142629	0	−0.15726	−0.09007	−0.29468	−0.47964
0	6.432420	2.058078	0	−0.58467	−1.02430	−0.24162	−0.43852
0	6.935301	2.948151	3	−0.32194	−0.38460	−0.16292	−0.30417
3	6.682532	2.971689	3	−0.69547	−1.21658	−0.20476	−0.40735
3	7.340776	3.266819	6	−0.37948	−0.65165	−0.28905	−0.49647
0	6.246628	2.975211	1	−0.63170	−0.91868	−0.18933	−0.39496
1	6.935301	3.808387	1	−0.39943	−0.82565	−0.21254	−0.40652
0	7.155994	3.790876	0	0.033046	0.025315	−0.25511	−0.45144
0	3.749303	4.037275	0	0.057784	0.065864	−0.22702	−0.47645
0	3.749303	4.486000	0	−0.22015	−0.32077	−0.23116	−0.43307
0	3.749303	4.521512	0	−0.22015	−0.32077	−0.23116	−0.43307
3	3.996920	4.342947	3	−0.58288	−1.01051	−0.25004	−0.46760
3	3.948311	3.749303	3	−1.56647	−0.51336	−0.25477	−0.49772
0	4.434671	3.892938	1	−1.35820	−0.36561	−0.43403	−0.22156
0	3.808387	3.897507	0	−0.47888	0.313824	−0.42404	−0.31154
0	6.246628	3.749303	0	−0.37719	−0.10301	−0.42728	−0.25119

ological activities similar tothat of the training set.

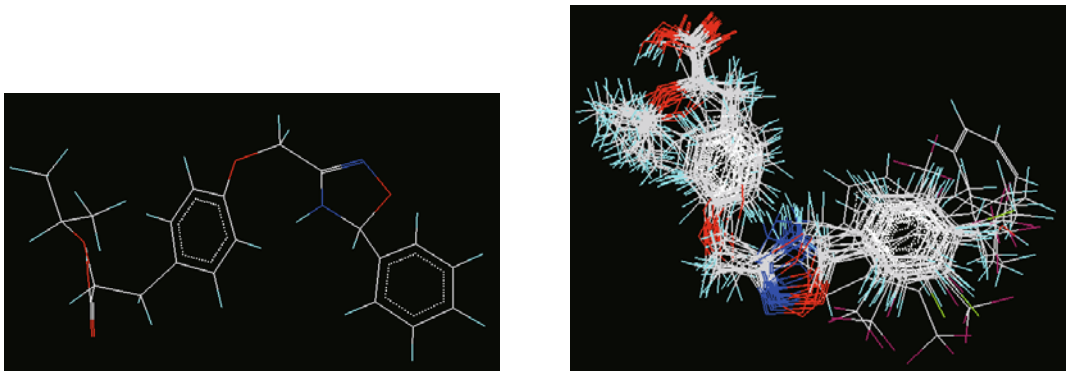
2.2.1 Two dimensional QSAR

2D-QSAR study requires the calculation of moleculardescriptors; almost 239 physicochemical descriptors were calculated by QSAR Plus module within VLife MDS. The invariable descriptors (descriptors that are constant for allthe molecules) were removed; as they do not contribute tothe QSAR. The various alignment-independent descriptors (Baumann, 2000) were also calculated. In this study to calculate AI descriptors, we have used following attributes, 2 (double bonded atom), 3 (triple bonded atom), C, N, O, S, H, F, Cl, Br and I and the distance range of 0–7.

2.2.2 Three dimensional QSAR

For generation of 3D QSAR model, *k Nearest Neighbor* Molecular Field Analysis (kNN MFA) method was used in conjunction with genetic algorithms (GA) and simulated annealing (SA) coupled with PLS and alignment of the molecules was carried out using template based alignment. The steps involved in 3D-QSAR studies are data selection, descriptor evaluation, structure alignment, selection of training and test set, variable selection, statistical methods, model evaluation and model interpretation.

All molecules in the dataset were aligned by template-based method (Ajmani *et al.*, 2006) where a template is built by considering common substructures in the series. The structure of α-isopropoxy phenylpropanoic acids template is shown in Fig. 1(a). The superimposition of all molecules based on minimizing root mean square deviation (RMSD) is shown in Fig. 1(b). The resulting alignments of molecules were used for building 3D models. For calculation of 3D field descriptor values, using *Tripos force field* (Clark *et al.*, 1989) steric and electrostatic field types, with cut-offs of 10.0 and 30.0 kcal/mol, respectively, were selected and charge type was selected as by Gasteiger and Marsilli (Gasteiger and Marsilli, 1980). The dielectric constant was set to 1.0 considering the distance dependent dielectric function. This resulted in calculation of 3400 field descriptors (1700 for each steric and electrostatic) for all the compounds in separate columns (Bhatia *et al.*, 2012).



(a) (b)

Fig. 1 (a) Common template used for alignment; (b) Alignment pattern of all 26 compounds as training set used for QSAR study.

2.2.3 Pharmacophore identification studies

A set of pharmacophore hypotheses was generated by the mole sign module of Vlife MDS 3.5 on the reported α-isopropoxy phenylpropanoic acids derivatives. All 26 aligned molecules were taken for pharmacophore development. Select the most active molecule to set it as reference. The reference molecule is the molecule on which the other molecules of the align dataset get aligned. For four point pharmacophore identification tolerance limit set up to 30 Å and max distance allowed between two features, setthe value to 5 Å. The pharmacophore model has to describe the nature of the functional groups like hydrogen bond donors and acceptors, charge interactions, and hydrophobic areas involved in ligand-target interactions, as well as the type of the non-covalent bonding and inter change distances.

2.3 k-Nearest Neighbor Molecular Field Analysis

3D-QSAR studies were carried out by *k-NN* method using genetic algorithms (GA) and simulated annealing (SA) coupled with PLS method. Among several search algorithms, genetic algorithms (GA) based feature selectionprocedures is the most popular for building QSAR models and can explain the situation more effectively (Hasegawa *et al.*, 1999).

Genetic algorithms (GA) described by Holland, is a stochastic optimization technique that mimic natural evolution andselection (Holland, 1992). The GA begins by generating a set of randomsolutions (the population), which are analogous to a set ofchromosomes in a biological system. The set of variablesindicated with a value of 1 in the chromosome is then used asinput for model building by partial least square method.

Simulated annealing (Zheng and Tropsha, 2000) is a multivariate optimization technique based on the Metropolis Monte Carlo algorithm for examining the equations of state and frozen states of n-body systems. The concept is based on the manner in which liquids freeze or metals recrystalise in the process of annealing. In simulated annealing, the process starts from an initial state of very high temperature and introduces perturbations, or random moves, which create a new state.

$$d = r^2(V^{new}) - r^2(V^{old}) \text{ is calculated}$$

If $d > 0$, V^{new} is accepted, else, it is accepted with probability exp (-d/T), where Tstands for temperature control parameter. The overall idea is tostart with a high value of T, so that all steps are accepted and thengradually reduce T as the simulation progresses, so that eventuallyonly steps that improve the solutions are accepted.

Internal validations of the models in all the cases are madein terms of cross-validated Q^2 and external predictability of the developed models are performed by calculating predictive R^2 (R_pred^2) using the following equations (Leach and Gillet, 2003).

$$q^2 = 1 - \frac{\sum(y_i - \hat{y}_i)^2}{\sum(y_i - y_{mean})^2} \quad (1)$$

where y_i and $\hat{y}_i$ are the actual and predicted activities of the i^{th} molecule, respectively, and y_{mean} is the average activity of all molecules in the training set. A model is considered acceptable when the value of Q^2 exceeds 0.5.

$$\text{Pred\_r}^2 = 1 - \frac{\sum(y_i - \hat{y}_i)^2}{\sum(y_i - y_{mean})^2} \quad (2)$$

In Eq. (2), where y_i and $\hat{y}_i$ are the actual and predicted activities of the i^{th} molecule in test set, respectively, and y_{mean} is the average activity of all molecules in the training set. The $pred\_r^2$ value is indicative of the predictive power of the current kNN–MFA model for external test set. For a predictive QSAR model, the value of R^2 pred should be more than 0.5.

PLS was employed as a statistical method for the evaluation of fitness in the genetic algorithms and simulated annealing scheme. PLS have been widely employed to solve multivariate structure-activity relationships in QSAR. The final model obtained is further refined by removing descriptors which do not affect predictive accuracy significantly.

3 Results and discussion

Two and Three dimensional quantitative structure-activity relationship studies of oxadiazole-substituted α-isopropoxy phenylpropanoic acids derivatives having inhibitory activities against with dual agonist PPARα and PPARγ activity have been performed using GA and SA based variable selection methods for developing PLS models respectively. The training and test sets selected for such study are the same as has been considered in 3D QSAR models for an effective comparison between GA and SA methodologies.

3.1 Modelling with genetic algorithm (PPARα) method

pIC$_{50}$(PPARα) = +0.6782(±0.1413) SsClcount + 0.4274 (±0.0964) T_N_F_2 - 0.5485 (±0.0094) SddsN (nitro) count + 0.8625 (±0.0278) SsOHcount + 0.85243

Optimum Components = 4, Degrees of Freedom = 18, $N_{training}$ = 20, N_{test}= 6, r^2= 0.8725, q^2= 0.7957, F test 40.865, r^2se = 0.1848, q^2 se = 0.2582, pred_r^2 = 0.8136, pred_r^2se = 0.1094.

The statistically significant model 1 using the genetic algorithm Partial least square (GA-PLS) method with 0.8725 as the coefficient of determination (r^2) was considered. Model-1 can explain 87% of the variance in the observed activity values. It shows cross-validated squared correlation coefficient (q^2 = 0.7957) of 79% and a predictivity for the external test set (pred_r^2 = 0.8136) of about 81%. The developed genetic algorithm-PLS model reveals that the descriptor is SddsN (nitro) count are inversely proportional to the activity and suggests the total number of nitro group connected with one single and two double bonds R position will lead to improved activity. Model-1 shows the positive contribution of SsOHcount indices for total number of -OH group connected with one single bond showed positive contribution. Such positive effect indicated that the activity was increased with the presence of hydroxy groups in 4th position in Phenylpropanoic moiety. The descriptor T_N_F_2 (∼15%) reveals the importance of presence of fluorine atom (i.e. –F, CF_3) at 2, 3 and 4th position site R on Phenylpropanoic nucleus to be detrimental for the activity.Thus, the presence of fluoro substituents (like in compound **2, 3, 9, 10, 13, 14**, and **21-26**) would increase the activity. The study revealed that SsClcount is topological parameter signifies the total number of chlorine atoms connected with one single bond and positive coefficient of the descriptor suggests that activity of Phenylpropanoic derivatives may be improved by increasing the number of chlorine atoms present in the Phenylpropanoic nucleus at R site. Thus, the presence of chloro substituents (like in compounds **7, 18**, and **19**) would increase the antihyperglycemic activity. The plots of actual activity *vs* predicted activity values of pIC$_{50}$ and contribution chart are shown in Fig. 2(a) and 2(b). The correlation matrix is shown in Table 3 which shows good correlation of selected parameters with biological activity. The predicted activities of the compounds by the above model are shown in Table 4.

pIC$_{50}$(PPARα) = E_602 (0.0484, 2.0340) - S_747 (−0.7153, −0.7111) - S_247 (−0.4907, −0.4588) - E_802 (−1.2877, −1.4138)

Degrees of Freedom = 22, $N_{training}$ = 20, N_{test} = 6, Optimum Components = 3, q^2 = 0.7188, F test = 32.652, r^2_se q^2_se = 0.3542, pred_r^2 = 0.7508.

For 3D-QSAR, a kNN-MFA with *genetic algorithm* Partial least square was used resulted in several statistically significant models, of which the corresponding best model with activity PPARα is reported herein. The *kNN*-MFA contour plots which showed the relative position and ranges of the corresponding important steric and electrostatic fields in the model, provided guidelines for new molecule design.The Stereo view of the super imposedmolecules along with the descriptors contributing tothe activity are shown in Fig. 2(c). Table 4 lists the predicted activity and the descriptor values. From 3D-QSAR model it is observed that the presence of steric descriptor S_747 and S_247 with negative values is also near from the R position of the Phenylpropanoic ring which indicates that less steric or less

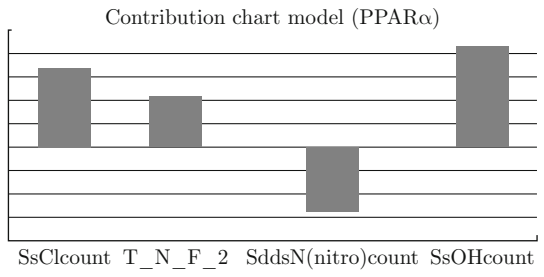
Table 3 Correlation matrix between descriptors present in the best QSAR model PPARα

Parameter	pIC$_{50}$	SsClcount	T_N_F_2	SddsN (nitro) count	SsOHcount
pIC$_{50}$	1.0000				
SsClcount	0.4376	1.0000			
T_N_F_2	0.6521	0.7698	1.0000		
SddsN (nitro) count	0.4876	0.6541	0.7863	1.0000	
SsOHcount	0.2317	0.5873	0.6983	0.8317	1.0000

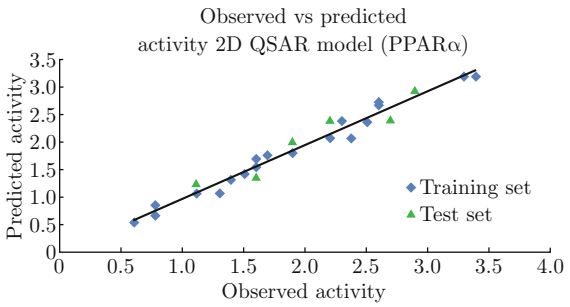
Table 4 Comparative Observed and Predicted Activities of phenylpropionic derivatives (PPARα and PPARγ)

Com. No	pIC_{50} (PPARα)	pIC_{50} (PPARγ)	2D QSAR model (PPARα)		3D GA-PLS model (PPARα)		2D-QSAR model (PPARγ)		3D SA-PLS model (PPARγ) (PPARγ)	
			Pred.	Res.	Pred.	Res.	Pred.	Res.	Pred.	Res.
1	2.204	1.897	2.073	0.131	2.376	−0.172	1.985	−0.880	1.833	0.064
2	1.897	2.000	1.793	0.104	1.962	−0.065	2.074	−0.074	2.092	−0.092
3	2.204	2.301	2.417	−0.213	2.368	−0.164	2.384	−0.083	2.427	−0.126
4	1.602	2.000	1.556	0.046	1.534	0.068	2.038	−0.038	1.915	0.085
5	1.897	1.698	2.023	−0.126	1.826	0.071	1.564	0.134	1.582	0.116
6	1.397	1.204	1.319	0.078	1.304	0.093	1.312	−0.108	1.168	0.036
7	1.113	1.301	1.052	0.061	1.254	−0.141	1.413	−0.112	1.395	−0.094
8	1.602	1.505	1.542	0.060	1.551	0.051	1.622	−0.117	1.435	0.070
9	1.505	1.397	1.416	0.089	1.698	−0.193	1.304	0.093	1.472	−0.075
10	1.301	1.799	1.075	0.226	1.162	0.139	1.887	−0.088	1.827	−0.028
11	1.113	0.602	1.275	−0.162	1.232	−0.119	0.544	0.058	0.689	−0.087
12	1.602	0.477	1.687	−0.085	1.868	−0.226	0.413	0.064	0.527	−0.050
13	1.602	2.000	1.379	0.223	1.441	0.161	2.102	−0.102	1.911	0.089
14	0.778	1.505	0.657	0.121	0.712	0.066	1.568	−0.063	1.618	−0.113
15	2.380	2.361	2.063	0.317	2.263	0.117	2.415	−0.054	2.212	0.149
16	3.301	1.113	3.181	0.120	3.464	−0.163	1.058	0.055	1.421	−0.308
17	2.698	0.301	2.417	0.281	2.641	0.057	0.338	−0.037	0.378	−0.077
18	2.897	1.602	2.958	−0.061	2.768	0.129	1.676	−0.074	1.545	0.057
19	2.602	1.397	2.665	−0.063	2.503	0.099	1.521	−0.124	1.268	0.129
20	2.505	0.602	2.363	0.142	2.433	0.072	0.525	0.077	0.674	−0.072
21	2.301	0.778	2.376	−0.075	2.253	0.048	0.727	0.051	0.695	0.083
22	2.602	2.204	2.718	−0.116	2.668	−0.066	2.113	0.091	2.283	−0.079
23	1.698	0.602	1.756	−0.058	1.663	0.035	0.683	−0.081	0.672	−0.070
24	0.778	1.505	0.851	−0.073	0.714	0.064	1.451	0.054	1.461	0.044
25	0.602	1.505	0.542	0.060	0.498	0.104	1.542	−0.037	1.483	0.022
26	3.397	2.799	3.176	0.221	3.462	−0.065	2.834	−0.035	2.749	0.050

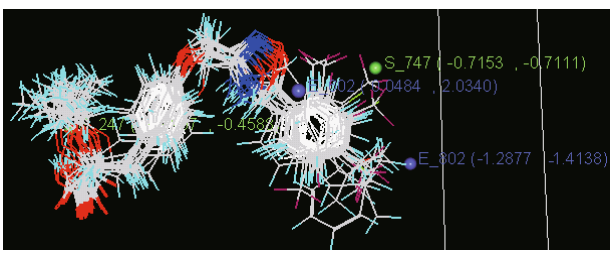
Res. = Obs. pIC_{50}–Pred. pIC_{50}



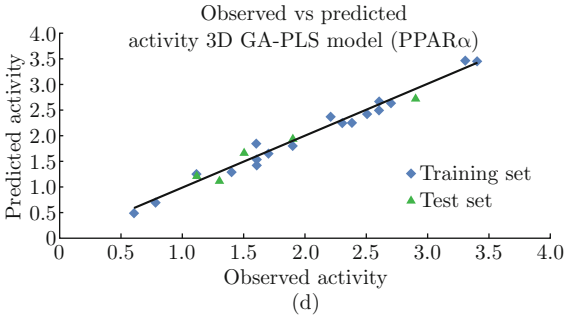
(a)



(b)



(c)



(d)

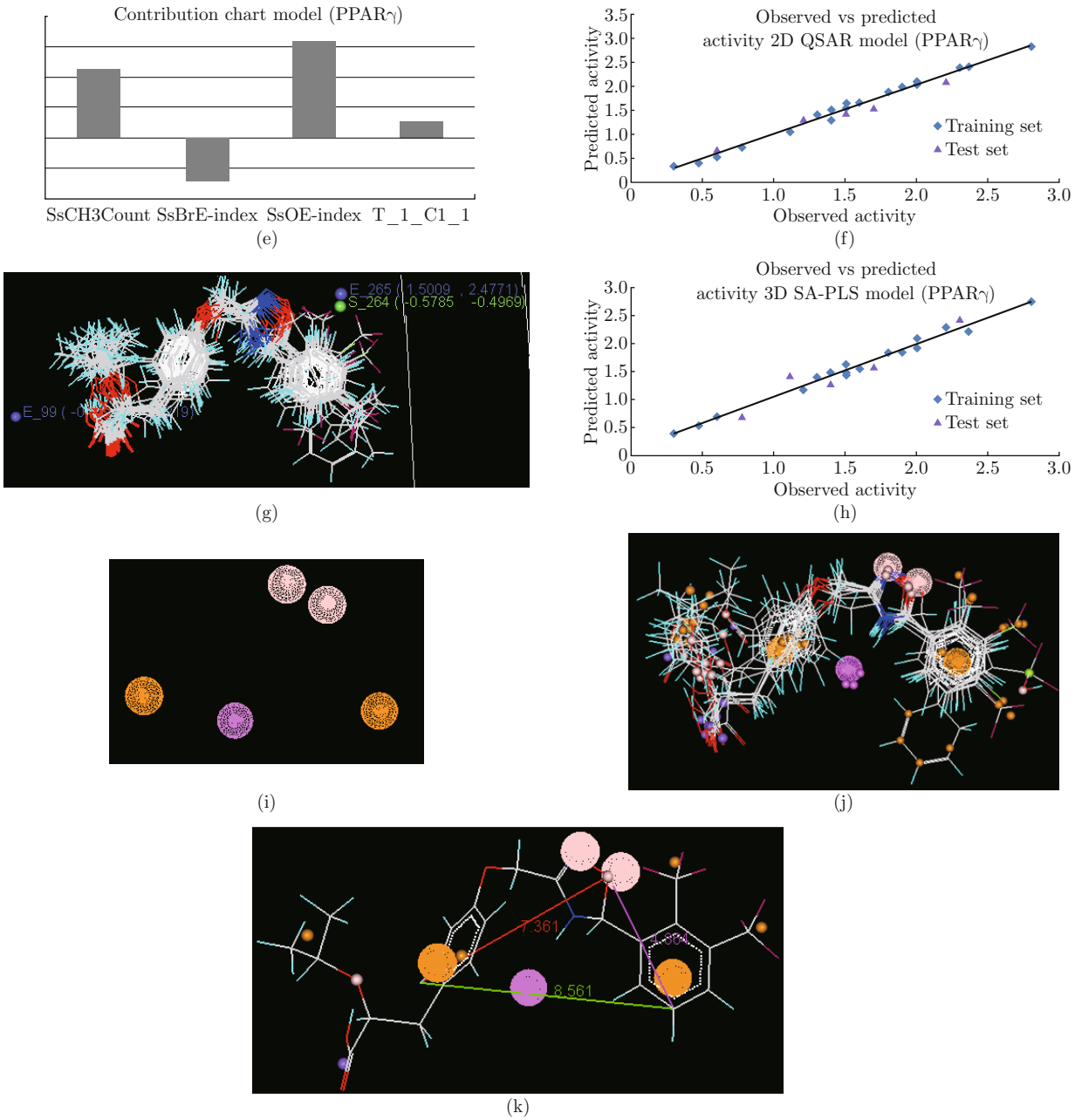


Fig. 2 (a) Plot of contribution chart of 2D QSAR Model (PPARα); (b) Graphs of observed *vs.* predicted activity of 2D QSAR model (PPARα); (c) Stereo view of the molecular rectangular field grid around the superposed molecular of phenylpropanoic acids derivatives (PPARα) compounds using GA-PLS kNN-MFA method; (d) Graphs of observed *vs.* predicted activity of 3D QSAR model (PPARα); (e) Plot of contribution chart of 2D QSAR Model (PPARγ); (f) Graphs of observed *vs.* predicted activity of 2D QSAR model (PPARγ); (g) Stereo view of the molecular rectangular field grid around the superposed molecular of phenylpropanoic acids derivatives (PPARγ) compounds using SA-PLS kNN-MFA method; (h) Graphs of observed *vs.* predicted activity of 3D QSAR model (PPARγ); (i) Pharmacophore features Substituted Phenylpropanoic Acids; (j) Aligned 3D pharmacophore features; (k) Probable best pharmacophore features of active molecule.

bulky substituent's are favorable on this site and presence of less steric substituents increases the antihyperglycemic activity of Phenylpropanoic compounds. It is observed that electrostatic descriptors like E_602 with positive coefficient are at the R ring of Phenylpropanoic structure indicating that electropositive groups are favorable on this site and presence of electropositive groups would increase the antihyperglycemic activity of

these compounds. Most of the active compounds in series (like in compound **4, 5, 6, 11**, and **12**) having electropositive substitution at the 3rd position of Phenylpropanoic ring strongly support the above statement. This is also well supported by 2D-QSAR study. Another electrostatic descriptor E_802 with negative coefficients are at the R ring of Phenylpropanoic structure indicating that electronegative groups are favorable on this site and presence of electronegative groups would increase the antihyperglycemic activity of these compounds. The graph of observed versus predicted activity for given set of molecules is shown in Fig. 2(d). The predicted (LOO) activities of the compounds by the above model are shown in Table 4.

3.2 Modelling with simulated annealing (PPARγ) method

pIC50 (PPARγ) = 0.4486(±0.0917)$SsCH_3$Count-0.2815(±0.0512) SsBrE-index + 0.6310 (±0.2815) SssOE-index +0.1067(±0.0047) T_1_Cl_1 - 0.0036

Optimum Components = 3, $N_{training}$ = 20, N_{test} = 6, r^2 = 0.7614, q^2 = 0.6996, F test =29.653, r^2 se = 0.2036, q^2 se = 0.2502, pred_r^2 = 0.7193, pred_r^2se = 0.3206, Z Score $Q^{\wedge 2}$ = 1.4334, Best Rand $Q^{\wedge 2}$ = 1.07212.

The statistically significant tetra-parametric model with simulated annealing Partial least square (SA-PLS) method with coefficient of determination (r^2) = 0.7614 is capable of explaining 76% of variance in the observed activity values. The model showed an internal predictive power (q^2 = 0.6996) of 69% and predictivity for external test set (pred_r^2 = 0.7193) about 72%. The F-test = 29.653 shows the overall statistical significance level of 99.99% of the model which means the probability of failure of the model is 1 in 10 000. The developed simulated annealing-PLS model reveals that the descriptor SsBrE-index reveals the importance of presence of number of Bromine connected with one single bond (i.e. -Br) at R position on ring to be detrimental for the activity. The descriptor $SsCH_3$Count was found to be directly proportional to the activity. This indicates that increase in $SsCH_3$Countof fragment R may lead to an increase in the activity. The positive coefficient of this descriptor signifies the importance of methyl group for activity. The above results are in close agreement with the experimental observations where compounds **4, 5, 6, 8, 11** and **12** with substituent at the R positions produce activity. The next descriptor T_1_Cl_1 is the number of double-bonded atoms separated fromthe chlorine atom by single bond. It is another influential alignment-independent descriptor (∼25% contribution), suggesting that the presence of substituents with chlorine on the phenyl ring at the ortho position will lead to an increase inactivity. It is evident that the chlorine atom attach 3rd and 4th position of R substituent (compound **7, 19** and **20**) increases the activity.The other descriptor such as SssOE-index which is topological indices for number of oxygen atom connected with two single bonds showed positive contribution and positive effect indicated that the activity was increased with the presence of methoxy groups. The results of activity depicted that the presence of electron donating group, OCH_3, in compound, increase the activities.The contribution chartfor all the descriptors in the QSAR model equation is illustrated in Fig. 2(e) and observed versus predicted activity of both test set and training set are portrayed in Fig. 2(f). The predicted (LOO) activities of the compounds by the above model are shown in Table 4. The correlation matrix is shown in Table 5 which shows good correlation of selected parameters with biological activity.

pIC_{50} (PPARγ) = E_265 (1.5009, 2.4771) - E_99 (−0.4218, −0.3219) - S_264 (−0.5785, −0.4969)

Degrees of Freedom = 20, $N_{training}$ = 20, N_{test} = 6, Optimum Components = 3, q^2 = 0.6421, F test = 24.731, q^2_se = 0.4317, pred_r^2 = 0.6732

3D-QSAR models were selected based on value of statistical parameters and the best SA- PLS 3D-QSAR model has a q^2 of 0.6421 and pred_r^2 of 0.6732. In Model as shown in Fig. 2(g) Positive range of electrostatic field descriptor indicates that the electrostatic potential E_265 (1.5009, 2.4771) is favorable for increase in activity and hence a less electro-negative substituent group is preferred in that region. From 3D-QSAR model Fig. 2(g)-it is observed that electrostatic field with negative coefficient E_99 (−0.4218, −0.3219) is far from the Phenylpropanoic moiety, indicating that electronegative groups are unfavorable on this site and presence ofelectronegative groups decrease the activity of Phenylpropanoic compounds. Negative values of steric S_264 descriptor negative range (green) indicate that negative steric potential is favorable for activity and less bulky substituents group is preferred inthat region.The predicted (LOO) activities of the compounds by the above model are shown in Table 4. The graph of observed versus predicted activity for given set of molecules is shown in Fig. 2(h).

3.3 Pharmacophore Identification Studies

A set of pharmacophore hypothesis was generated using the mole sign module of V life MDS 3.5 on the reported Substituted α-Isopropoxy Phenylpropanoic Acids. Each hypothesis was found to contain common features like hydrogen bond donor, hydrogen bond acceptor, and aromatic features (Fig. 2(i)). The pharmacophore hypothesis generated in V life MDS 3.5 (Fig. 2(j)) indicated the significance of presence of two aromatic features for the antihyperglycemic activity; these features are contributed by the Phenylpropanoic Acids nucleus. Existence of such a pharmacophoric pattern is the condition for ligand–macromolecule interaction, and such searches for chemical patterns in molecular databases allow us to find new scaffolds for devel-

Table 5 Correlation matrix between descriptors present in the QSAR model PPARγ

Parameter	pIC_{50}	$SsCH_3Count$	SsBrE-index	SssOE-index	T_1_Cl_1
pIC_{50}	1.0000				
$SsCH_3Count$	0.3198	1.0000			
SsBrE-index	0.3764	0.4543	1.0000		
SssOE-index	0.3658	0.5896	0.6745	1.0000	
T_1_Cl_1	0.3376	0.4097	0.6487	0.7243	1.0000

oping lead structures (Choudhari and Bhatia, 2012). From distance geometry studies of the pharmacophore, it is clear that for optimum factor antihyperglycemic activity, the distance between the two hydrophobic features should be about (62HAc 37H) = 7.3613 Å, Distance (62HAc 26C) = 4.8637 Å, Distance (37H 26C) = 8.5606 Å, Distance (62HAc 19N) = 1.4307 Å and Distance (21O 54H) = 3.1729 Å the distance between the hydrogen bonddonor, acceptor and two aromatic features (Fig. 2(k)). The average RMSD of the pharmacophore alignment of each two molecules is 0.6549 Å.

4 Conclusion

The present studies were aimed at deriving predictive 2D, 3D-QSAR model and Pharmacophore studies capable of elucidating the structural requirements for novel oxadiazole-substituted α-isopropoxy phenylpropanoic acids with dual agonist PPARα and PPARγ activity.The suitable set of the molecular descriptors was calculated and the important descriptors using the variable selections of the genetic algorithm and simulated annealing were selected. A comparison between the attained results indicated the superiority of the genetic algorithm over the simulated annealing method in the feature-selection. The predictive quality of the quantitative structure-activity relationship models was tested for an external set of six compounds, sphere exclusion method out of 26 compounds. The genetic algorithm-PLS model with four selected descriptors was obtained. This model, demonstrating high statistical qualities r^2= 0.8725, q^2= 0.7957, and pred_r^2 = 0.8136 could predict the model antihyperglycemic activity of the PPARα molecules. The results suggest that nitro, hydroxy group connected with one single and two double bonds R position will lead to improved activity. Furthermore, visualization of the 3D-QSAR model using kNN-MFA method combined with various selection procedures. By using kNN-MFA approach, various 3D QSAR models were generated to study the effect of steric and electrostatic descriptors on antihyperglycemic activity. It was found that the (E_602) electropositive groups like ethyl were essential R site in Phenylpropanoic moiety for potent antihyperglycemic activity. The 2D- and 3D-QSAR results revealed that that the presence of chloro or fluoro substituents would increase the antihyperglycemic activity and presence of bulky electron withdrawing groups at 3^{rd} and 4^{th} position of ring would increase the antihyperglycemic activity. The QSAR model suggests that electron withdrawing character is crucial for the antihyperglycemic. In addition to the electron withdrawing character, hydrogen bond donating group, acceptors andaromatic groups positively contribute to the antihyperglycemic. These findings provide a set of guidelines for designing compounds with better antihyperglycemicpotential.

Acknowledgment

The author thanks Vlife Science Technologies Pvt. Ltd for providing the trial version software for the study.

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