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Exploring Structural Requirements For PPARγ Modulation Of Benzoyl 2-Methyl Indoles Using Physico-Chemical Parameters

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Abstract: Peroxisome proliferator-activated receptor *gamma* (PPARγ) has been the focus of intense research, as ligands for this receptor have emerged as potent insulin sensitizers used in the treatment of type 2 diabetes mellitus (T2DM). A series of benzoyl 2-methyl indoles was subjected to quantitative structure-activity relationship (QSAR) analysis. The studies showed that the electronic properties, energy of lowest unoccupied molecular orbital (E_{LUMO}) and dipole moment (DPL), and principal moment of inertia-*Z* component (PMI-*Z*) of the molecule can be explored to design potent PPARγ modulators. LUMO, which is indicative of π-bonding interaction of species crucial for the electrophilicity of the molecules, suggested that molecules are able to interact with electron-rich area at the receptor site. DPL is related to the molecular charge distribution in Z-component and can be altered through the incorporation of electronegative group. The QSAR study provides important structural insights in designing of potent PPARγ modulators.
Keywords: peroxisome proliferator-activated receptor (PPAR), type 2 diabetes mellitus (T2DM), quantitative structure activity relationship analysis (QSAR), indoles, selective PPARγ modulators.

Introduction

The peroxisome proliferator-activated receptor *gamma* (PPARγ) has been the focus of intense research during the past decade because ligands for this receptor have emerged as potent insulin sensitizers used in the treatment of type 2 diabetes mellitus (T2DM). Increased levels of circulating free fatty acids and lipid accumulation in non-adipose tissue have been implicated in the development of insulin resistance. This situation is improved by PPARγ ligands, which improve the insulin sensitivity.[1] Between 1997 and 1999, a new class of drugs called 'glitazones'[2] was approved by the FDA for the treatment of type 2 diabetes. These agents are PPARγ modulators, share a common partial chemical structure: thiazolidine-2,4-diones (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. Glitazones, while efficacious, exhibit significant liabilities; they are associated with edema and weight gain in man. In addition, cardiac hypertrophy is observed in preclinical rodent models. These adverse effects preclude glitazones from being used as frontline therapy in T2DM, suggesting that pursuit of a safer second-generation human PPARγ (hPPARγ) agonist is desirable.

Selective PPARγ modulators (SPPAR γMs), which are also known as hPPARγ partial agonists, have recently attracted much interest. Selective modulation of the hPPARγ could provide significant anti-diabetic activity while concurrently reducing or eliminating PPARγ-mediated side-

effects.[3-5] We therefore initiated a search for non-TZD PPARγ ligands with the goal of finding novel insulin sensitizers. Owing to continuing zeal in exploring the structural insights to aid the design of safer novel insulin sensitizers[6-10], our research has been tuned to cater the needs of changing scenario of anti-diabetic therapy. In this context QSAR analysis of Benzoyl 2-methyl indoles[11] as selective PPARγ modulators was performed to identify the associated molecular properties, which are responsible for drug-receptor interactions.

Materials and Methods

The in vitro activity data of PPARγ by benzoyl indoles (Table 1) were taken from the reported work[11]. The biological activity data (IC_{50} in μ*M*) was converted into negative logarithmic dose (pIC_{50}) for QSAR analysis to reduce skewness of data set.

The series was subjected to molecular modeling and QSAR studies using CS Chem-Office Software version 6.0[12] running on a P-III processor. Energy minimization was carried out using molecular mechanics (MM2) until the root mean square (RMS) gradient value became smaller than 0.1 kcal/mol Å. Minimized molecule was subjected to re-optimization via the Hamiltonians approximations using Austin model-1 (AM1) method until the RMS gradient became smaller than 0.0001 kcal/mol Å[13]. The geometry optimization of the lowest energy structure was carried by Chem3D ultra version 6.0 using Eigenvector following (EF) routine. The descriptor values for all the molecules were calculated using "compute properties module" of program.

All the descriptor values for the molecules considered as independent variables and PPARγ binding data (pIC50) were taken as dependent variable. Sequential multiple linear regression analysis method was used to develop tri-variant relationship between pIC_{50} and descriptors.

Calculated thermodynamic descriptors included critical temperature (T_c), ideal gas thermal capacity (C_p), critical pressure (P_c), boiling point (BP), Henry's law constant (H), stretch bend energy (E_{SB}), bend energy (E_B) and log P.

Steric descriptors derived were Connolly accessible area (SAS), Connolly molecular area (CMA), Connolly solvent excluded volume (CSEV), exact mass (EM), molecular weight (MW), principal moment of inertia-X component (PMI-*X*), principal moment of inertia-Y component (PMI-*Y*) and principal moment of inertia-Z component (PMI-*Z*), molar refractivity (MR) and ovality (OVAL).

Electronic descriptors, such as electronic energy (E_{Elc}), highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), X-component of dipole moment (DPL_X), Y-component of dipole moment (DPL_Y), Z-component of dipole moment (DPL_Z), resultant dipole moment (*DPL*), repulsion energy (E_{NR}), VDW-1,4- energy (E_{14}), Non-1, 4-VDW energy (E_V) and total energy (*E*) were calculated.

Sequential multiple linear regression analysis method was used to perform QSAR analysis employing in-house program VALSTAT[14]. In sequential multiple regression, the program searches for all permutations and combinations sequentially for the data set. Here, it searched for 7,770 combinations and gave multi-variant equations, based on squared correlation coefficient. The ± data within the parentheses are the standard error, associated with coefficient of the descriptors in regression equations. The best model was selected on the basis of various statistical parameters such as correlation coefficient (r), standard error of estimation (SE), sequential Fischer test (F), bootstrapping squared correlation coefficient (r_{bs}^2), bootstrapping standard deviation (S_{bs}) cross-validated squared correlation coefficient (q^2) and randomization test (chance).

Results and Discussion

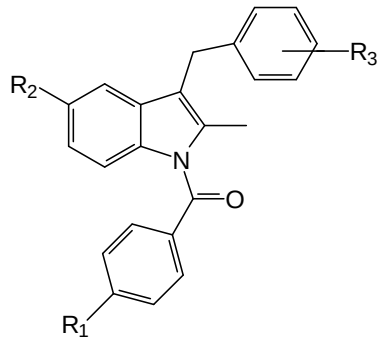
All the descriptor values for the molecules were considered as independent variables and pIC_{50} was taken as dependent variable. Sequential multiple linear regression analysis method was used to develop tri-variant relationship between pIC_{50} and descriptors. When data set was subjected to sequential multiple linear regression analysis, in order to develop QSAR model, various statistically significant equations with coefficient of correlation ($r \geq 0.92$) were obtained (Table 2 and 3). Equation 1 was considered as model (Table 4 and Fig. 1).

$$pIC_{50} = 0.164 + 6.746e\text{-}005*PMI\text{-}Z + 0.434*DPL + 3.709*E_{LUMO}$$

$n = 17$, $r = 0.937$, $r^2 = 0.878$, $SE = 0.480$, $F = 31.145$, $q^2 = 0.802$

The model having good correlation coefficient value explains 87.8% variance in the activity. The standard error of estimation (SE = 0.480) and a higher F value rendering the model statistically significant. The data showed overall better statistical significance >99.9% with $F_{(3,13)}$ = 31.145 against the tabulated value for sequential Fischer test at 99.9% significant ($F_{(3,13\alpha\ 0.001)}$= 11.9). The inter-correlations of the descriptor in the model were low, indicating that all the

Table 1—Structure and *in-vitro* activity of benzyl Indoles



Compd.	R_1	R_2	R_3	IC_{50} (μM)[a]	pIC_{50}
1	Cl	OCH_3	2-COOH	6.28	5.202
2	Cl	OCH_3	3-COOH	0.208	6.682
3	Cl	OCH_3	4-COOH	4.69	5.329
4	Cl	OCH_3	2-OCH_2COOH	0.333	6.478
5	Cl	OCH_3	3-OCH_2COOH	0.099	7.004
6	Cl	OCH_3	2-OCH(Me)COOH	0.084	7.076
7	Cl	OCH_3	3-OCH(Me)COOH	0.049	7.310
8	Cl	OCH_3	4-OCH(Me)COOH	2.14	5.670
9	Cl	OCH_3	2-$OC(Me)_2COOH$	0.079	7.102
10	Cl	OCH_3	3-$OC(Me)_2COOH$	0.045	7.347
11	Cl	OCH_3	4-$OC(Me)_2COOH$	0.914	6.039
12	OCH_3	OCF_3	2-OCH(Me)COOH	0.023	7.638
13	OCH_3	OCF_3	2-OCH(Me)COOH	0.002	8.699
14	OCH_3	OCF_3	2-$OC(Me)_2COOH$	0.001	9
15	OCH_3	OCF_3	3-OCH(Me)COOH	0.001	9
16	OCH_3	OCF_3	3-OCH(Me)COOH	0.003	8.523
17	OCH_3	OCF_3	3-$OC(Me)_2COOH$	0.003	8.523

[a] Average of two experiments. Data presented as mean ± SEM

descriptors were contributing independently to the biological activity. The contribution of descriptors to model is in the ratio PMI-*Z*: *DPL*: E_{LUMO}: 3.822: 1: 1.479 in normalized data.

The model was subjected to leave-one-out cross-validation method, The value of cross-validated squared correlation co-efficient (q^2= 0.802), predictive residual sum of square (S_{PRESS}= 0.612) and standard error of predictivity (S_{DEP}= 0.535) suggested good predictive ability of the biological activity. The bootstrapping squared correlation coefficient (r^2_{bs}=0.886) suggested the robustness of the model and contribution of molecular descriptor values of each molecule to the correlation was nearly same. Randomized biological activity data test (chance <0.001) revealed that the result was not based on chance correlation. The QSAR Study revealed that E_{LUMO}, PMI-*Z* and Dipole were the principle descriptors contributed positively for the PPARγ modulator activity. E_{LUMO}, indicative of π-bonding interaction, is crucial for the electrophilicity of the molecules, suggested that molecules are able to interact with electron-rich area at the receptor site. Dipole, related to the molecular charge distribution, can be altered through the incorporation of electronegative group. PMI-*Z*, Principle Moments of Inertia-Z component, suggests the orientation of the aromatic ring bearing bulkier substitution along Z-axis for better activity.

The QSAR Study revealed that electronegative substitution, which enhances electrophilicity of the molecule, with orientation of the aromatic ring bearing bulkier substitution along Z-axis, could be helpful in designing the Selective PPARγ modulators for the management of type 2 diabetes mellitus.

Table 2—QSAR statistics of significant equations

Eqn. no.	Regression Equations	r^2	SE	F	ICWP (Up to)	r^2_{bs}	S_{bs}	Chance	Outlier	q^2	S_{PRESS}	S_{DEP}
1	pIC_{50}=0.164+6.746e-005*PMI-*Z* +0.434**DPL* +3.709*E_{LUMO}	0.878	0.480	31.145	0.485	0.894	0.067	<0.001	Nil	0.801	0.612	0.635
2	pIC_{50}=44.331-0.088*BP+0.062*CAA -7.643e-005*PMI-X	0.877	0.483	30.639	0.845	0.906	0.044	<0.001	Nil	0.781	0.643	0.562
3	pIC_{50}=1.969-0.002*HF+5.899e-005* PMI-Y-0.329*SE	0.863	0.509	27.206	0.828	0.892	0.066	<0.001	Nil	0.753	0.683	0.597
4	pIC_{50}=3.474+3.985e-005*PMI-Y +1.175*E_{LUMO} +0.114*DDE	0.861	0.512	26.773	0.786	0.902	0.061	<0.001	Nil	0.749	0.688	0.602
5	pIC_{50}=58.029-0.066*CT+0.039* CMA +6.583e-005*PMI-Y	0.859	0.515	26.472	0.878	0.894	0.065	<0.001	Nil	0.734	0.708	0.619

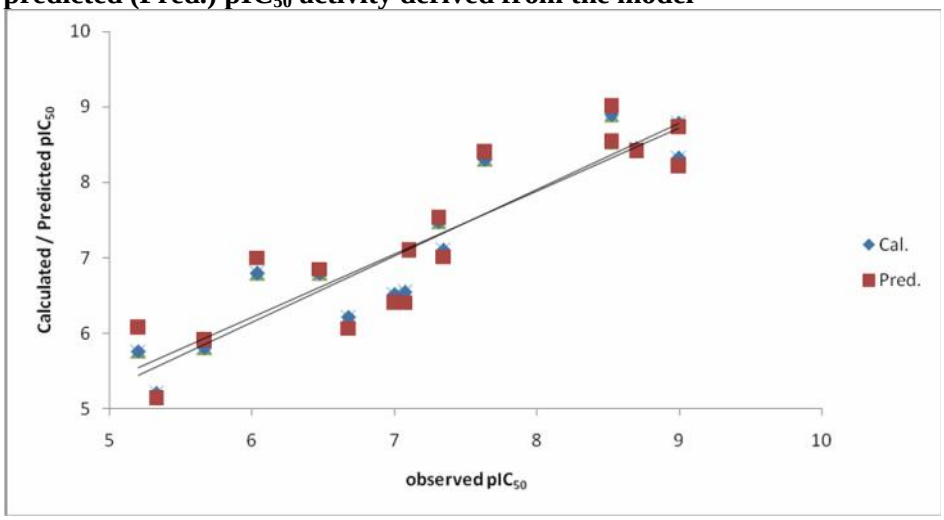
Table 3—Inter-correlation matrix of parameters used in QSAR model

	PMI-*Z*	*DPL*	E_{LUMO}
PMI-*Z*	1		
DPL	0.225	1	
E_{LUMO}	0.156	0.486	1

Table 4—Observed (Obs.), calculated (Cal.) and leave-one-out predicted (Pred.) pIC_{50} data of

Compd.	pIC_{50}			Z-Score	Residual	
	Obs	Cal.	Pred.			
1	5.202	5.764	6.075	-1.299	0.562	0.873
2	6.682	6.219	6.067	1.071	-0.463	-0.615
3	5.329	5.201	5.139	0.295	-0.128	-0.19
4	6.478	6.795	6.850	-0.733	0.317	0.372
5	7.004	6.523	6.404	1.114	-0.481	-0.6
6	7.076	6.540	6.411	1.239	-0.536	-0.665
7	7.310	7.479	7.527	-0.391	0.169	0.217
8	5.670	5.807	5.911	-0.319	0.137	0.241
9	7.102	7.100	7.100	0.005	-0.002	-0.002
10	7.347	7.100	7.015	0.570	-0.247	-0.332
11	6.039	6.796	7.004	-1.750	0.757	0.965
12	7.638	8.307	8.402	-1.546	0.669	0.764
13	8.699	8.456	8.415	0.563	-0.243	-0.284
14	9	8.780	8.731	0.508	-0.22	-0.269
15	9	8.328	8.207	1.555	-0.672	-0.793
16	8.523	8.533	8.537	-0.022	0.01	0.014
17	8.523	8.895	9.005	-0.860	0.372	0.482

Fig. 1—Scatter plot of observed versus calculated (Cal.) and leave-one-out predicted (Pred.) pIC_{50} activity derived from the model



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