World Journal of Pharmaceutical and Life Sciences
WJPLS

www.wjpls.org SJIF Impact Factor: 4.223

QSAR STUDIES ON 2-PHENYL-ETHENESULFONIC ACID PHENYL ESTERS AS PPARγ AGONISTS

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Article Received on 30/12/2016 Article Revised on 19/01/2017 Article Accepted on 09/02/2017

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ABSTRACT

Metabolic disorders, such as obesity and type 2 diabetes, have assumed epidemic proportions and present major challenges for healthcare systems. We have tried to explore the series of 2-phenyl-ethenesulfonic acid phenyl esters to develop best QSAR equations by which we can design novel and potent compounds. The QSAR study carried out on thirteen 2-phenyl-ethenesulfonic acid phenyl esters as PPARγ agonist. Molecular modeling studies were performed using chemoffice 6.0 supplied by Cambridge soft. The sketched structures were subjected to energy minimization & the lowest energy structure was used to calculate the physiochemical properties. The regression analysis was carried out using a computer program called VALSTAT. The best models were selected from the various statistically significant equations. The study revealed that the Model-3 explains 83.1% variance in the PPARγ binding activity. Model-3 having low standard error (0.0901) shows the relative good fitness of the model. It has the characters of large F value (37.6459), low P- value (0.00217), r^2 and q^2 values close to 1, as well as $p<0.001$. It means model-3 is a best model among all developed model. It shows that descriptor molecular weight (MW) and connolly solvent-excluded volume (Angstroms3) (SEV) contribute negatively; whereas molar refractivity (MR) contribute positively towards PPARγ binding activity. Molar refractivity (MR), a steric parameter, which is positively correlated, indicates that sterically bulky substituent would increases the binding affinity.

KEYWORDS: PPARγ; Diabetes; ethenesulfonic acid phenyl esters; QSAR.

1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia, altered metabolism of lipids, carbohydrates, proteins and an increased risk of complications from vascular diseases.[1,2] Diabetes is a major degenerative disease in the world today.[3] Several epidemiological and clinical studies indicate a direct relationship between hyperglycemia and long-term complications such as retinopathy, nephropathy, neuropathy and angiopathy, etc.[4,5] The disease which is characterized by hyperglycemia[6], lipoprotein abnormalities,[7] raised basal metabolic rate,[8] defect in reactive oxygen species scavenging enzymes[9] and high oxidative stress-induced damage to pancreatic beta cells.[10,11] Insulin resistance in the liver and peripheral tissues together with a pancreatic cell defect are the common causes of type 2 diabetes. It is now appreciated that insulin resistance can result from a defect in the insulin receptor signaling system, at a site post binding of insulin to its receptor.[12]

Diabetic patients (>90) suffer from type 2 diabeties, that is non insulin diabetic mellitus, which is characterized by insulin resistance and hyperglycemia.[13] Diabetic is a major and growing public health problem throughout the world, with an estimated worldwide prevalence in 2000 of 150 million people, excepted to rice to 220 million people by 2010.[14] The various pharmacological active compounds such as sulfonylureas, the first generation of antidiabetic agents such as chlorpropamide, tolbutamide and tolazamide are still in use but are less potent than the second generation drugs like glibenclamide, glipizide and glimepiride. Sulfonylureas are mostly subjected to hepatic metabolism, yielding less active or inactive metabolites that are then eliminated through the kidneys. Patients with impaired hepatic or renal function risk severe hypoglycemia because of accumulation of active drug in circulation.[15,16]

Intensive effort has been invested in the development of drugs involving PPARγ agonists as therapeutic agents.[17] Over the past several years, PPAR-γ modulators have attracted increasing attention as potential treatments of diabetes. In fact, using various animal models, the thiazolidinedione, rosiglitazone (a full PPARγ agonist), was shown to reduce bone mineral density and increase bone marrow adipocytes.[18] Thus, we have tried to explore the series of 2-phenyl-ethenesulfonic acid phenyl esters as PPARγ agonist to develop best QSAR equations by which we can design novel and potent compounds.

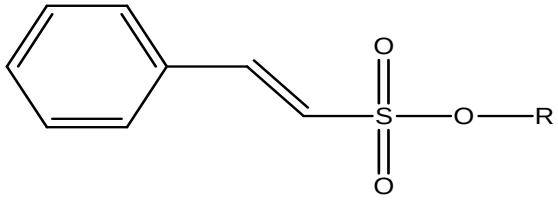
2. MATERIALS AND METHOD

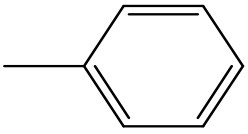
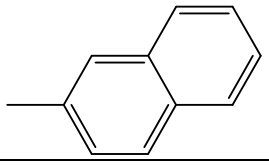
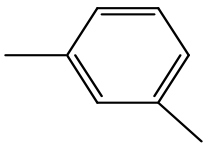
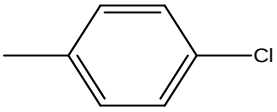
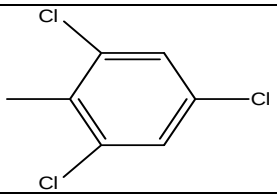
2.1 Data Set for Analysis

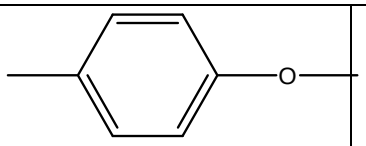
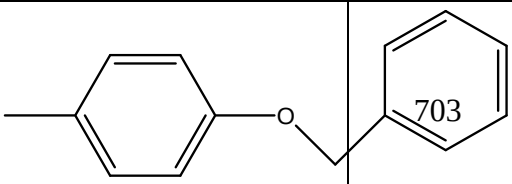
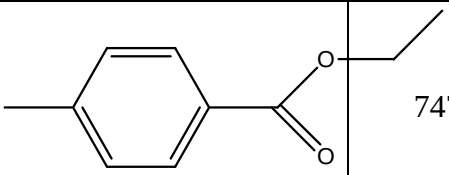
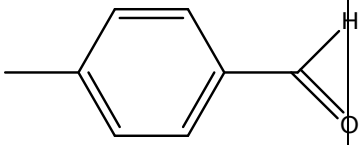
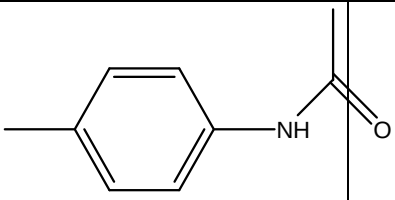
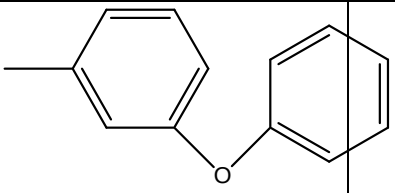
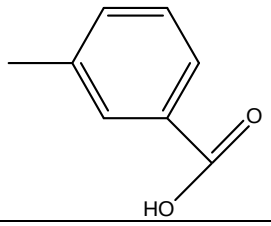
The in-vitro biological activity data reported as IC50 for PPARγ binding of 2-phenyl-ethenesulfonic acid phenyl ester compounds was used for the current study.[19] A total of 13 compounds were selected for the study. The structures and binding data of 2-phenyl-ethenesulfonic acid phenyl esters are shown in Table 1. As biological activities are generally skewed, the reported IC_{50} (in mole) values were converted into the corresponding pIC_{50} using the following formula.

$pIC_{50} = -\log IC_{50}$

Table 1: Structures and biological activity values for PPARγ binding for 2-phenyl-ethenesulfonic acid phenyl esters.



Compound	R_1	PPARγ (IC_{50} nM)	Observed BA (pIC_{50})
1a		1326	5.877456
1b		1088	5.963371
1c		407	6.390406
1d*		1187	5.925549
1e		302	6.519993
1f		1439	5.841939

1g		1294	5.888066
1h*		703	6.153045
1i		747	6.126679
1j		2098	5.678195
1k*		10712	4.970129
1l		382	6.417937
1m		13521	4.868991

IC_{50} = Dose in nM required to produce 50% binding

*Molecules in test set (03 compounds), remaining in training set (10 compounds)

2.2 Software

An Intel Pentium dual personal computer (CPU at 2.22 GHz) with the Windows XP operating system was used. QSAR study was performed in software ChemOffice 6.0, Cambridgesoft, USA).[20] Sketching of structures was performed with ChemDraw ultra 6.0

and geometry optimisation was performed with Chem3D Ultra and was utilized to calculate the molecular descriptors. The VALSTAT software was employed for the Pearson Correlation Matrix and simple multiple linear regression model (MLR) analysis.[21]

2.3 Molecular Modelling

The structures were sketched using ChemDraw Ultra 6.0 and were exported to Chem3D software. The molecular mechanics (MM_2) method was applied to search for lower energy conformation for each molecule. The energy minimised molecules were subjected to re-optimization via the Austin model -1 method until the root mean square gradient attained a value smaller than 0.001 kcal/mol using Molecular Orbital Property Accompany Name (MOPAC).

2.4 Descriptors Generation

The thermodynamic, steric and electronic parameters are shown in table 2 were calculated for QSAR analysis. Thermodynamics parameters describe free energy change during drug receptor complex formation. Spatial parameters were quantified for steric features of drug molecules required for its complimentary fit with the receptor. Electronic parameters describe weak non-covalent bonding between drug molecules and the receptor.[22]

Table 2: List of descriptors used in QSAR analysis.

S.No.	Descriptors	Abbr.	Type	Description
1	Bend Energy (kcal/mol)	Eb	T*	The sum of the angle-bending terms of the force-field equation.
2	Dipole-Dipole Energy (kcal/mol)	Ed	T*	The sum of the electrostatic energy terms resulting from interaction of two dipoles.
3	Partition Coefficient	CLogP	T*	Partition Coefficient (Octanol/water)
4	Stretch Energy	Es	T	Represents the energy associated with distorting bonds from their optimal length.
5	Stretch-Bend Energy(kcal/mol)	Esb	T*	The sum of the stretchbend coupling terms of the force-field equation.
6	Torsion Energy(kcal/mol)	Et	T*	The sum of the dihedral bond rotational energy term of the force-field equation.
7	Total Energy (kcal/mol)	E	T*	The sum of all terms the the force-field equation.
8	van der Waals 1.4 Energy (kcal/mol)	E14	T*	The sum of pairwise van der Waals interaction energy terms for atoms separated by exactly 3 chemical bonds.
9	Boiling Point (Kelvin)	Bp	T*	The boiling point for the structure at 1 atm.
10	Heat of Formation (kcals/mole)	HF	T*	The heat of formation (ΔHf) for the structure at 298.15 K and 1 atm.
11	LogP	LogP	T*	The logarithm of the partition coefficient for n-octanol/water.
12	Molar Refractivity (cm3/mole)	MR	T*	The molar refraction index.

13	Connolly Solvent Accessible Surface Area (Angstroms2)	SAS	Steric	The locus of the center of a spherical probe (representing the solvent) as it is rolled over the molecular model.
14	Connolly Molecular Surface Area (Angstroms2)	MSS	Steric	The contact surface created when a spherical probe sphere (representing the solvent) is rolled over the molecular model.
15	Connolly Solvent-Excluded Volume (Angstroms3)	SEV	Steric	The volume contained within the contact molecular surface.
16	Ovality	Ovality	Steric	The ratio of the CMA to the Minimum Surface Area. The Minimum Surface Area is the surface area of a sphere having a volume equal to the CSE of the molecule. Computed from the CMA and CSE properties.
17	Principal Moments of Inertia-X	PMIX	Steric	The Moments of Inertia when the Cartesian coordinate axes are the principal axes of the molecule.
18	Principal Moments of Inertia-Y	PMIY	Steric	The Moments of Inertia when the Cartesian coordinate axes are the principal axes of the molecule.
19	Principal Moments of Inertia-Z	PMIZ	Steric	The Moments of Inertia when the Cartesian coordinate axes are the principal axes of the molecule.
20	Electronic Energy	EE	E*	The total electronic energy.
21	Gamma polarizability	Gpol	E*	Third order polarizability coefficients.
22	HOMO Energy(eV)	HOMO	E*	Energy of the highest occupied molecular orbital.
23	LUMO Energy (eV)	LUMO	E*	Energy in of the lowest unoccupied molecular orbital.
24	Repulsion Energy (eV)	RE	E*	Total core-core internuclear repulsion between atoms.
25	Dipole Moment	Dipole	E*	Molecular dipole moment.

T*= Thermodynamic property, E*= Electronic property

2.5 Division of Test and Training Set

It is proven that the only way to estimate the true predictive power of a model is to test it on a sufficiently large collection of compounds from an external test set. The test set must include not less than five compounds, whose activities and structure must cover the range of activities and structures of compounds from the training set. This application is necessary for obtaining trustful statistics for comparison between the observed and predictive activities for these compounds. In this series 3 compounds were selected as a test set and remaining 10 compounds were used as training set. The test set used for the validation of model.

2.6 Statistical Analysis

First, the descriptors were checked for constant or near constant values and those detected were discarded from the original data matrix. Then, the descriptors were correlated with each

other and with the activity data. Among the collinear descriptors detected, the one most highly correlated with activity was retained and the rest were omitted. The contribution of descriptors to biological activity was studied using simple linear regression analysis by VALSTAT Software and, due to the problem of collinearity among descriptors, different combinations of descriptors were subjected to sequential and stepwise multiple regression analysis. The intercorrelation matrix of the descriptors of QSAR equations is given in table 3. Descriptors having intercorrelation above |r|>0.5 were not considered while deriving the QSAR model. The predictor variables with p value >0.05 were eliminated whilst deriving the QSAR models in order to assure their statistical reliability. Statistical quality of the models was evaluated by using the parameters; number of compounds (n), correlation coefficient (r), coefficient of determination (r^2), standard error of estimate (s), variance, Fischer F-test for quality of fit, and Student's t-test for test of significance . Figures within parentheses indicate the confidence interval (95% significant) of the regression coefficient and the intercept. The level of significance of each regression term was assessed using t-test and is reflected through the minimum value of the standard error term. Residual plots derived by plotting residuals, i.e., the difference between the predicted and the observed response as a function of the dependent variable, are used to identify outliers from the QSAR models. A compound is considered as an outlier when the residual value exceeds twice the standard error of the estimate of the model.

Table 3: Pearson Correlation Matrix of the descriptors used in all models.

Parameters	BA	E14	MR	SEV	PMIX	HOMO	LUMO
BA	1.000						
E14	-0.174	1.000					
MR	0.159	-0.284	1.000				
SEV	-0.225	-0.080	-0.060	1.000			
PMIX	0.229	-0.252	0.456	0.084	1.000		
HOMO	0.328	-0.182	0.300	0.776	0.094	1.000	
LUMO	0.342	-0.050	-0.159	0.388	-0.277	0.439	1.000

In order to validate the derived QSAR models, the leave-one-out (LOO) method, also known as the jack-knife validation test, was used. Once a model was derived, each compound was eliminated from the remaining compounds and the eliminated compound was predicted from this model. The same procedure was repeated after elimination of another compound, until all the compounds had been eliminated once. The predictability of each model was evaluated by using cross validated correlation coefficient (q^2).[23]

3. RESULT AND DISCUSSION

The correlation between the different physicochemical descriptors as independent variable and the negative log of the observed activity as dependent variable was determined using VALSTAT while exploring the statistically significant relationships to study the selectivity requisites among these compounds. The intercorrelation between all the descriptors was also checked and good orthogonality was ensured during quantitative model building. Some of the statistically significant models are discussed below.

Model 1: BA = [29.8216 (± 3.81837)] +HOMO [2.76231 (± 0.431208)] +E14 [3.69903 (± 1.42212)] +PMIX [-8.30969 (± 3.39441)]

N = 10, r = 0.7815, r2 = 0.6107, r2adj = 0.5690, std = 0.3911, F = 14.6409

Model 1 explains only 61.2% variance in the PPARγ binding activity. It shows that descriptor highest occupied molecular orbital (HOMO) and van der Waals 1.4 Energy (kcal/mol) (E14) contribute positively, where as principal moment of inertia X (PMIX) contribute negatively towards PPARγ binding activity. It is not a very good significant equation therefore new model required having good explained variance.

Model 2: BA = [3.21588 (± 1.27474)] +LUMO [0.010452 (± 0.00158041)] +SEV [-0.0442412 (± 0.00871579)] +MR [0.18273 (± 0.0241215)]

N = 10, r = 0.830432, r2 = 0.6896, r2adj = 0.65513, std = 0.281289, F = 19.9964

Model 2 explains only 68.9% variance in the PPARγ binding activity. It shows that descriptor connolly solvent-excluded volume (Angstroms3) (SEV) contribute negatively; whereas low unoccupied molecular orbital (LUMO) and Molar refractivity (MR) contributes positively towards PPARγ binding activity. In this model one compound (1e) was outlier. It is not a very good significant equation therefore new model required having good explained variance. So we tried to develop the new model by removing the outlier.

Model 3: BA = [3.87157(± 0.429843)] +LUMO[0.0040636(± 0.000697125)] +SEV [-0.0243882 (± 0.00313334)] +MR [0.0947197 (± 0.010074)]

N = 09, r = 0.9115, r2 = 0.8309, r2adj = 0.8087, std = 0.0901, F = 37.6459, q2 = 0.7641

Model 3 explains 83.1% variance in the PPARγ binding activity. Model 3 having low standard error (0.0901) shows the relative good fitness of the model. It has the characters of large F value (37.6459), low P- value (0.00217), r^2 and q^2 values close to 1, as well as $p<0.001$. It means model-4 is a best model among all developed model. It shows that

descriptor connolly solvent-excluded volume (Angstroms3) (SEV) contribute negatively; whereas low unoccupied molecular orbital (LUMO) and Molar refractivity (MR) contributes positively towards PPARγ binding activity. The LUMO energy is the crucial indicator of molecular reactivity and properties. The positive contribution of LUMO indicates its high value will favor the activity. The significance of LUMO indicates, high electrophilicity of the compounds, and there by accepting electrons to its lowest unoccupied molecular orbital, would help them to improve the biological activity. Molar refractivity (MR), a steric parameter, which is positively correlated, indicates that sterically bulky substituent would increases the binding affinity. The graph plotted between observed and predicted biological activity (BA) of training set of model-3 is shown in figure 1.

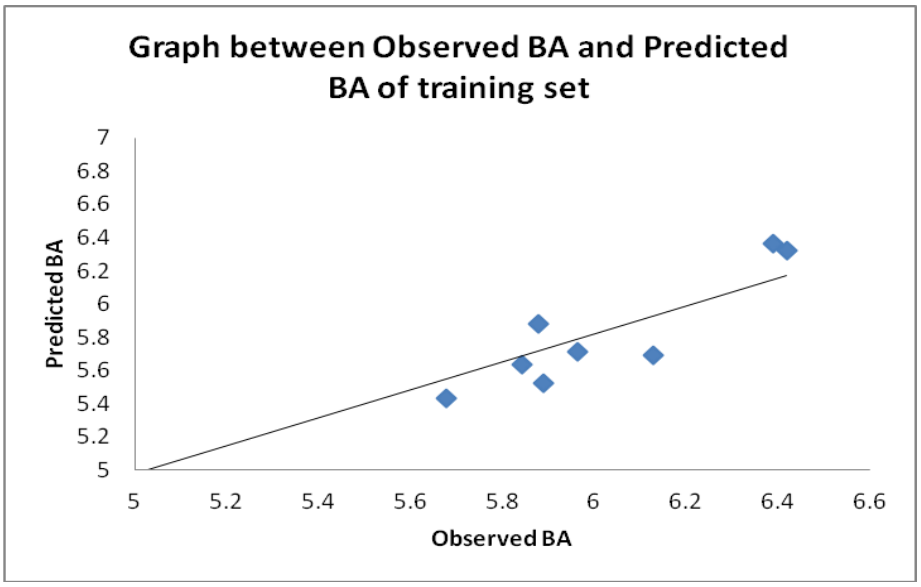


Figure 1: The graph plotted between observed and predicted biological activity (BA) of training set of model-3.

To conclude, all types of descriptors like electronic, thermodynamic, and steric must be fully optimized for better PPARγ binding activity. The findings suggests that the presence of bulky group increases the PPARγ binding activity, and the presence of high electrophilicity groups such as methoxy group increases the activity of the compound. The moiety which increases the charge distribution over the molecule is favourable for the activity. The present study provides better insight into designing more potent PPARγ agonists in future prior to their synthesis.

ACKNOWLEDGEMENTS

The authors wish to thank the Principal, Sadhu Vaswani College, Bhopal for providing the necessary facilities for undergoing this research work.

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