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QSAR analysis of thiazole benzenesulfonamide substituted 3-pyridylethanolamines as β_3-adrenergic receptor agonist

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Abstract—A quantitative structure–activity relationship study on a series of substituted benzene sulfonamide-3-pyridylethanolamines with β_3-adrenergic receptor agonist activity was made using a combination of various physiochemical descriptors. Several significant equations with good co-efficients of correlation ($\geqslant 0.930$) were obtained; the two models were selected using predictive ability of equations for test set. Both models highlight some common important structural features, that is, high electrostatic potential energy and the lipophilic nature of the molecule, favorable for β_3-adrenergic receptor agonist activity.

Obesity is a chronic disorder of energy imbalance in which a long-term excess of energy intake over expenditure leads to the storage of that excess energy as white adipose tissue.[1] The search for anti-obesity agents has become one of the most exciting areas in drug discovery. Subsequent to an enormous increase in the number of possible molecular targets, the focus has shifted from target identification to target validation. Because important biological functions such as the regulation of energy intake and expenditure are controlled by complex systems, an improved understanding of pathophysiology is a prerequisite for the selection and successful development of candidates for the treatment of obesity.[2] The past 25 years has seen a great increase in the incidence of obesity, both in the Western world and in developing Third-World countries. Despite the seemingly inexorable progression of this disease, there have been only limited advances in the pharmacotherapy of this condition. Of the newest introductions to the obesity drug portfolio, orlistat, which acts to prevent dietary fat absorption, and sibutramine, which seems to affect both arms of the energy balance equation, were the first new chemical entities to be introduced for the treatment of obesity in 30 years.[3] Currently available drugs include selective serotonin re-uptake inhibitors like fluoxetine, noradrenergic re-uptake inhibitors such as phentermine, a serotonin and noradrenergic re-uptake inhibitor (sibutramine), and an intestinal lipase inhibitor (orlistat). An active research program is underway to develop new agents based on the rapidly expanding knowledge of the complex mechanisms regulating body weight. Leptin, a hormone produced by adipocytes that inhibits food intake, has undergone clinical trials and analogs are currently being developed. Other agents include amylin, melanocortin-4 receptor agonists, neuropeptide Y antagonists, β_3-adrenergic receptor (β_3-AR) agonists, and glucagon-like peptide-1 agonists.[4] β-Adrenergic agents have been generally classified into β_1, β_2, and β_3 receptor-specific subtypes. Agonists of β-receptors promote the activation of adenyl cyclase. Activation of β_3 receptors is

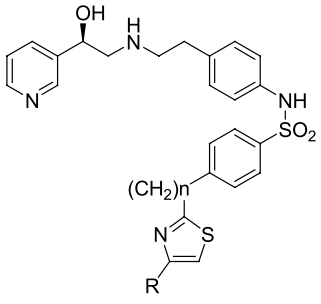

Figure 1. Lead compound for the present study.

Keywords: Anti-hyperlipidemic agents; QSAR (quantitative structure–activity relationship); β_3-adrenergic receptor agonist; Substituted benzene sulfonamide-3-pyridylethanolamines.
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known to stimulate lipolysis (e.g., the breakdown of adipose tissue triglycerides into glycerol and fatty acids) and metabolic rate (energy expenditure), thereby promoting the loss of fat mass. In addition, compounds that are β_3-AR agonists have hypoglycemic activity.[5,6] The mitochondrial uncoupling protein (UCP) is usually expressed only in brown adipose tissue (BAT) and a key molecule for metabolic thermogenesis. Chronic stimulation of β_3-AR induces ectopic expression of UCP in adipose tissues conventionally considered as white fat and even in skeletal muscle, which probably contributes to the potent anti-obesity effect of the β_3-AR agonist. Heat production in BAT is a significant component of whole body energy expenditure, and its dysfunction contributes to the development of obesity.[7] Agonists specific to β_3-AR stimulate lipolysis and BAT thermogenesis and may be useful as an anti-obesity drug.[8] We identified in the literature 32 molecules in development: 9 molecules are in the discovery phase, 5 molecules are in different clinical phases, 10 molecules were discontinued, and for 8 molecules no development was reported.[1] Here we report quantitative structure–activity relationship (QSAR) studies of such β_3-AR agonists. In the present work even if no conclusive therapeutic agents have been identified, with the huge recent increase in our knowledge on the molecular modeling processes involved in drug design, we have tried to identify the associated molecular properties and exploited them to optimize β_3-AR agonist activity.

The β_3-adrenergic receptor agonist activity data of 3-pyridylethanolamine derivatives were taken from the reported work of Mathvink et al.[9] (Fig. 1, Tables 1 and 2). The biological activity data (EC_{50} in nm) were converted to negative logarithmic dose (pEC_{50}) for quantitative structure–activity relationship (QSAR) analysis. The molecular modeling study was performed using a P-III processor using MOE[10] and using the regression analysis program VALSTAT.[11] The molecular structures of all 23 compounds were sketched using the builder module software and energy minimized via steepest descent, conjugative gradient, and truncated Newton methods in sequence using MMFF94 as force field with energy tolerance value of root mean square gradient 0.001 kcal/mol and maximum number of iteration set to 1000. Conformational search of each energy-minimized structure was performed using the stochastic approach. The stochastic conformational search method is similar to the RIPS method, which generates new molecular conformation by randomly perturbing the position of each coordinate of each atom in the molecule followed by the energy minimization. All conformers generated for each structure were analyzed in conformational geometries panels with great care, and the lowest energy conformation of each structure was selected and added to a molecular database to compute various physicochemical properties from three classes: 2D-descriptors based on atoms and connection information of

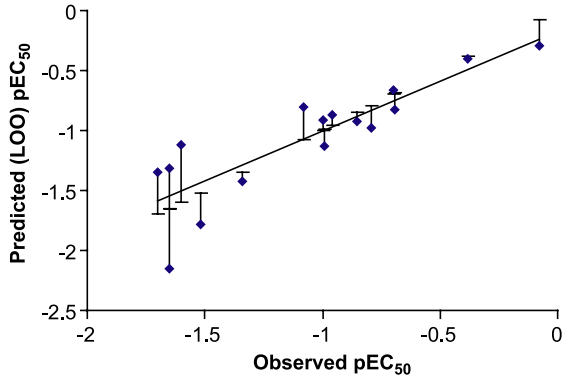


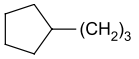
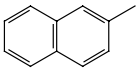
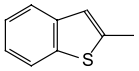
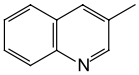
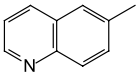
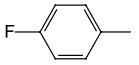
Figure 2. Plot between observed pEC_{50} and predicted (LOO) pEC_{50} with residual presentation for the training set using model-1.

Table 1. Structure and activities of thiazole benzenesulfonamide substituted 3-pyridylethanolamines used in the training set

S. No.	Comp. No.	*N*	R	EC_{50}[a]	pEC_{50}[b]
1	T-1	0	C_8H_{17}—	10	−1.000
2	T-2	0	$CH_3CONH(CH_2)_5$—	50	−1.699
3	T-3	0	—$(CH_2)_2$	33	−1.519
4	T-4	0	CH_2	5.0	−0.699
5	T-5	0	O	9.1	−0.959
6	T-6	0	NH	4.9	−0.690
7	T-7	0	N	40.0	−1.602
8	T-8	0	N	22.0	−1.342
9	T-9	0	F, F	7.1	−0.851
10	T-10	0	C_6H_{11}	1.2	−0.079
11	T-11	0	tBu	2.4	−0.380
12	T-12	0	HO	45.0	−1.653
13	T-13	0	CH_3CONH	45.0	−1.653
14	T-14	0	F, CH_2	6.2	−0.792
15	T-15	1	C_8H_{17}—	9.8	−0.991
16	T-16	1	CH_2	12.0	−1.079

[a] EC_{50} (in nM) in vitro ability of compounds to stimulate increases in cAMP in Chinese hamster ovary cells expressing the cloned human β_3-adrenergic receptor.
[b] Negative logarithmic EC_{50}.

Table 2. Structures and activities of thiazole benzenesulfonamide substituted 3-pyridylethanolamines used in the test set

S. No.	Comp. No.	*N*	R	EC_{50}[a]	pEC_{50}[b]
1	Test-1	0	C_6H_{13}—	51.0	−1.708
2	Test-2	0		26.0	−1.415
3	Test-3	0		2.0	−0.301
4	Test-4	0		5.8	−0.763
5	Test-5	0		7.3	−0.863
6	Test-6	0		2.7	−0.431
7	Test-7	0		9.5	−0.978

[a] EC_{50} (in nM) in vitro ability of compounds to stimulate increases in cAMP in Chinese hamster ovary cells expressing the cloned human β_3-adrenergic receptor.
[b] Negative logarithmic EC_{50}.

the molecules; i3D-descriptors used three-dimensional coordinate information about each molecule, which are invariant to rotations and translations of the conformation; and x3D descriptors which were supported by three-dimensional coordinate information require an absolute frame of reference using QuaSAR module.[12] The descriptor values used in the model generation are shown in Table 3.

The series was divided into a training set of 16 compounds and a test set of 7 compounds on the basis of structural diversity and cover the complete range of variation in agonist activity. The data were transferred to the statistical program in order to establish a correlation between physicochemical parameters as independent variables and β_3-adrenergic receptor agonist activity as dependent variable. The sequential multiple linear regression analysis method was employed. In sequential multiple regression, the program searches for all permutations and combinations sequentially for the data set. In this case it searched for 2,66,916 combinations and gave multi-variant equations based on squared correlation coefficient. The ± data within the parentheses are the standard deviations associated with the coefficient of descriptors in regression equations. The best model was selected from the various statistically significant equations on the basis of the observed squared correlation coefficient (r^2), the standard error of estimate (SE), the sequential Fischer test (F), the bootstrapping squared correlation coefficient (r^2_{bs}), the bootstrapping standard deviation (S_{bs}), the cross-validated squared correlation coefficient using leave-one-out procedure (r^2_{cv}), chance statistics (evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation), outliers (on the basis of Z-score value), and the predictive squared correlation coefficient of the test set (r^2_{pred}).

The training set was subjected to sequential multiple linear regression analysis, in order to establish a correlation between physicochemical parameters and β_3-adrenergic receptor agonist activity. Several significant equations with coefficients of correlation (r) $\geqslant 0.930$ were obtained, which account for more than 86.4% of the variance in the activity data. A high correlation coefficient alone is not enough to select the equation as a

Table 3. Calculated values of descriptors for compounds used in model 1 and model 2

Comp. No.	E_ele	Chi0	SlogP	SlogP_VSA0	SlogP_VSA8
T-1	−0.03886	28.91779	6.87004	43.39598	119.67910
T-2	−0.03887	29.08093	4.88707	61.40673	63.07386
T-3	−0.04619	28.49514	5.75221	43.39598	6.46865
T-4	−0.04033	30.35695	6.71104	43.39598	6.46865
T-5	−0.03845	28.94274	6.38027	43.39598	6.46865
T-6	−0.03770	28.94274	6.11537	43.39598	6.46865
T-7	−0.03709	27.08093	5.02907	43.39598	6.46865
T-8	−0.03878	27.08093	5.02907	43.39598	6.46865
T-9	−0.03845	28.82141	5.91227	43.39598	6.46865
T-10	−0.03868	31.48671	7.75684	43.39598	81.94227
T-11	−0.03753	30.45117	6.93157	43.39598	6.46865
T-12	−0.03857	27.95117	5.33967	68.78120	6.46865
T-13	−0.04969	30.23563	5.59247	43.39598	6.46865
T-14	−0.03848	28.65828	5.69694	43.39598	6.46865
T-15	−0.03690	29.62490	6.57593	61.40673	138.54750
T-16	−0.03900	31.06406	6.22120	61.40673	6.46865
Test-1	−0.04003	27.50358	6.08984	43.39598	81.94227
Test-2	−0.03813	28.65828	6.33584	43.39598	81.94227
Test-3	−0.03769	29.64984	6.78727	43.39598	6.46865
Test-4	−0.03836	28.94274	6.84877	43.39598	6.46865
Test-5	−0.03790	29.64984	6.18227	43.39598	6.46865
Test-6	−0.03888	29.64984	6.18227	43.39598	6.46865
Test-7	−0.04053	28.65828	5.69694	43.39598	6.46865

model and hence the internal consistency of the training set was confirmed using the leave-one-out (LOO) cross-validation method to ensure the robustness of the equations. Although a few equations showed good internal consistency (Q^2 = 0.700–0.802), they may not be applicable for the analogs which were never used in the generation of the correlation and therefore, the predictive power of Eqs. 1–6 was further confirmed by a test set of seven compounds.

$$\begin{aligned} \mathrm{pEC_{50}} &= 0.782(\pm 0.121)\log \mathrm{P(o/w)} \\ &\quad - 0.463(\pm 0.120)\mathrm{chi1v\_C} \\ &\quad - 0.042(\pm 0.013)\mathrm{vsa\_pol} + 0.169(\pm 0.688) \\ n &= 16,\ r^2 = 0.881,\ \mathrm{SE} = 0.187,\ F = 29.599 \end{aligned} \tag{1}$$

Equation 1 gave a high correlation coefficient, a significant F-value, a low standard deviation but showed significant deviation in the bootstrapping squared correlation coefficient, which indicates that the contribution of physiochemical parameters of one or more than one compound toward the correlation is either too high or too low. This implies that the model is not a proper representative of the group of analogs and this is further supported by a very poor predictivity of activity of the test set (r^2_{pred} = 0.019) (Table 4). Also the physiochemical parameters have a very high degree of dependency on each other (up to 0.935).

$$\begin{aligned} \mathrm{pEC_{50}} &= 3.670(\pm 1.003)\mathrm{a\_ICM} \\ &\quad - 0.012(\pm 0.004)\mathrm{PEOE\_VSA} - 0 \\ &\quad + 0.694(\pm 0.084)\mathrm{SlogP} - 9.832(\pm 1.888) \\ n &= 16,\ r^2 = 0.877,\ \mathrm{SE} = 0.190,\ F = 28.643 \end{aligned} \tag{2}$$

$$\begin{aligned} \mathrm{pEC_{50}} &= 2.404(\pm 0.963)\mathrm{a\_ICM} + 35.991(\pm 15.289)\mathrm{E\_ele} \\ &\quad + 0.640(\pm 0.089)\mathrm{SlogP} - 7.443(\pm 2.129) \\ n &= 16,\ r^2 = 0.865,\ \mathrm{SE} = 0.199,\ F = 25.549 \end{aligned} \tag{3}$$

Equations 2 and 3 are satisfactory for the bootstrapping squared correlation coefficient but the inter-correlation between parameters is high (up to 0.682), which revealed that the physicochemical parameters are dependent on each other, and also the prediction of activity of the test set was not significant.

$$\begin{aligned} \mathrm{pEC_{50}} &= 0.014(\pm 0.002)\mathrm{PEOE\_VSA\_NEG} \\ &\quad + 92.891(\pm 15.324)\mathrm{E\_ele} \\ &\quad - 0.028(\pm 0.006)\mathrm{SlogP\_VSA0} + 0.006(\pm 0.843) \\ n &= 16,\ r^2 = 0.872,\ \mathrm{SE} = 0.194,\ F = 27.214 \end{aligned} \tag{4}$$

Equation 4 fulfills many of the statistical validations such as the correlation co-efficient, the cross-validated squared correlation co-efficient, the predictive residual sum of square standard error of prediction, the bootstrapping squared correlation co-efficient and chance. The correlation accounted for more than 87.2% of the variance in the activity and also the inter-correlation among the parameters is less (<0.213). The data showed an overall internal statistical significance level better than 99.9% as $F_{(3,12\,\alpha\,0.001)}$ = 27.214 which exceeds the tabulated $F_{(3,12\,\alpha\,0.001)}$ = 12.7, the cross-validated squared correlation coefficient (Q^2 = 0.779), the predictive residual sum of square (S_{PRESS} = 0.254), and the standard error of prediction (S_{DEP} = 0.220) suggested good internal consistency as well as predictive ability of the biological activity with low S_{DEP}. The values of r^2_{bs} and s_{bs} are statistically significant, but the equation had low predictivity of the test set compounds compared to Eqs. 5 and 6.

$$\begin{aligned} \mathrm{pEC_{50}} &= 0.266(\pm 0.039)\mathrm{chi0} + 88.998(\pm 14.954)\mathrm{E\_ele} \\ &\quad - 0.030(\pm 0.006)\mathrm{SlogP\_VSA0} - 3.880(\pm 1.234) \\ n &= 16,\ r^2 = 0.876,\ \mathrm{SE} = 0.191,\ F = 28.303 \end{aligned} \tag{5}$$

$$\begin{aligned} \mathrm{pEC_{50}} &= 45.869(\pm 15.591)\mathrm{E\_ele} + 0.558(\pm 0.071)\mathrm{SlogP} \\ &\quad - 0.003(\pm 0.001)\mathrm{SlogP\_VSA8} - 2.526(\pm 0.777) \\ n &= 16,\ r^2 = 0.864,\ \mathrm{SE} = 0.200,\ F = 25.364 \end{aligned} \tag{6}$$

Equations 5 and 6 were quite significant, which showed a bootstrapping squared correlation coefficient value at par to the conventional r^2. The inter-correlation among the parameters (ICWP) was less than 0.213 and 0.418 for Eqs. 5 and 6, respectively (Table 5), which suggests insignificant or poor dependency of physicochemical parameters on each other. On the basis of various significant statistical validation data (Table 4) Eqs. 5 and 6 were selected as models 1 and 2, respectively, which may be a true representation in order to explore the factors responsible for the β_3-adrenergic receptor agonist

Table 4. QSAR statistics of significant equations

Equation No.	r^2	SE	F	ICAP[a] (Up to)	r^2_{bs}	s_{bs}	Chance	Q^2	S_{PRESS}	S_{DEP}	r^2_{pred}
1	0.881	0.187	29.599	0.935	FPE[b]	FPE[b]	0.001	0.762	0.264	0.229	0.019
2	0.877	0.190	28.643	0.682	0.879	0.069	0.001	0.802	0.241	0.208	0.171
3	0.865	0.199	25.549	0.682	0.872	0.071	0.001	0.786	0.251	0.217	0.374
4	0.872	0.194	27.214	0.213	0.878	0.087	0.001	0.779	0.254	0.220	0.402
5	0.876	0.191	28.303	0.213	0.901	0.063	0.001	0.712	0.291	0.252	0.598
6	0.864	0.200	25.364	0.418	0.866	0.073	0.001	0.798	0.243	0.211	0.485

[a] The maximum limit of inter-correlation among the descriptors used in the generation of equations.
[b] Floating point error.

activity of the series of analogs. This may be helpful in designing more potent substituted benzene sulfonamide 3-pyridylethanolamines.

Model 1 has a better correlation co-efficient ($r = 0.936$), which accounts for more than 87.6% of the variance in the activity, also the inter-correlation among the parameters is less (<0.213). The equation shows that in the multi-variant model, the dependent variable can be predicted from a linear combination of the independent variables. The P value is less than 0.001 for each physiochemical parameter involved in model generation. The data showed an overall internal statistical significance level better than 99.9% as it exceeded the tabulated $F_{(3,12\,\alpha\,0.001)} = 12.7$. The model was further tested for the outlier by the Z-score method and no compound was found to be an outlier (Table 6), which suggested that the model is able to explain the structurally diverse analogs and is helpful in designing more potent compounds using physiochemical parameters. The leave-one-out cross-validation method was employed for the prediction of activity (Fig. 2 and Table 6), and a Q^2 value (in the biological activity data of leave-one compound) of 0.3 corresponds to a confidence limit greater than 95%, which minimizes the risk of finding a significant explanatory equation for the biological activity just by mere chance. The cross-validated squared correlation coefficient ($Q^2 = 0.712$), predictive residual sum of square ($S_{PRESS} = 0.291$), and standard error of prediction ($S_{DEP} = 0.252$) suggested a good internal consistency as well as predictive ability of the biological activity with low S_{DEP}. The r^2_{bs} is at par with the conventional squared correlation coefficient (r^2). Randomized biological activity test (chance < 0.001) revealed that the results were not based on chance correlation. The robustness and wide applicability of the model were further explained by significant r^2_{pred} value (0.598) of test set data (Fig. 3 and Table 7). In general, the model fulfills the statistical validation criteria to a significant extent to be a useful theoretical base for proposing more active compounds. In Model-1 E_ele and chi0[13,14] contributed positively while SlogP_VSA0[15–17] contributed negatively, to the observed variance in activity. E_ele is representative of electrostatic potential energy, which is helpful for rationalizing the interaction between molecule and receptor surface, and chi0 is the Keir and Hall chi connectivity indices of zero order intended to model different aspects of molecular shape. Thus, reimproving chi0 and E_ele increases the agonist effect. SlogP_VSA0 is representative of accessible van der Waals surface area of atom or atoms of hydrophilic nature in the molecules and suggests that substitution of groups, which are less hydrophilic, might increase the biological activity. The study revealed that distal end substitutions may interact with a hydrophobic pocket at receptor site; hence substitutions which have polar functionality at the distal end

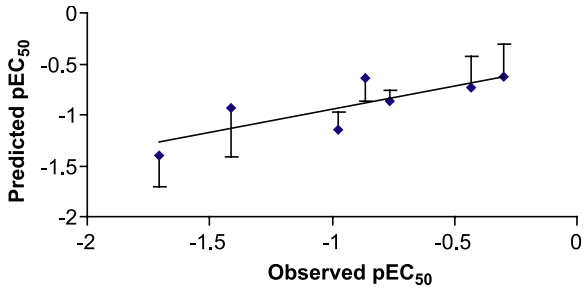


Figure 3. Plot between observed pEC_{50} and predicted pEC_{50} with residual presentation for the test set using model1.

Table 5. Correlation matrix of descriptors used in model

	SlogP	SlogP_VSA0	E_ele	SlogP_VSA8	chi0
SlogP	1.000				
SlogP_VSA0	0.244	1.000			
E_ele	0.160	0.213	1.000		
SlogP_VSA8	0.418	0.251	0.238	1.000	
Chi0	0.737	0.043	0.155	0.221	1.000

Table 6. Calculated and predicted pEC_{50} (by LOO) of training set with residual and Z-score value using model 1 and model 2

Comp. No.	Model 1					Model 2				
	Calculated pEC_{50}	Residual	Z-value	Predicted pEC_{50} (LOO)	Residual (LOO)	Calculated pEC_{50}	Residual	Z-value	Predicted pEC_{50} (LOO)	Residual (LOO)
T-1	−0.924	0.076	−0.443	−0.917	−0.083	−0.856	0.144	−0.804	−0.783	−0.217
T-2	−1.416	0.283	−1.660	−1.343	−0.356	−1.783	−0.084	0.470	−1.828	0.129
T-3	−1.689	−0.170	0.999	−1.785	0.266	−1.455	0.063	−0.354	−1.426	−0.092
T-4	−0.672	0.027	−0.161	−0.667	−0.032	−0.651	0.048	−0.266	−0.642	−0.057
T-5	−0.881	0.078	−0.457	−0.873	−0.086	−0.750	0.209	−1.170	−0.720	−0.239
T-6	−0.814	−0.124	0.727	−0.830	0.140	−0.863	−0.173	0.968	−0.887	0.196
T-7	−1.255	0.347	−2.032	−1.117	−0.485	−1.441	0.161	−0.899	−1.392	−0.210
T-8	−1.406	−0.063	0.372	−1.428	0.086	−1.519	−0.176	0.987	−1.559	0.217
T-9	−0.913	−0.062	0.361	−0.920	0.068	−1.011	−0.159	0.892	−1.028	0.176
T-10	−0.224	−0.145	0.851	−0.297	0.218	−0.233	−0.154	0.859	−0.324	0.245
T-11	−0.397	−0.017	0.099	−0.401	0.021	−0.400	−0.020	0.109	−0.406	0.026
T-12	−1.908	−0.255	1.494	−2.152	0.499	−1.336	0.317	−1.775	−1.287	−0.366
T-13	−1.537	0.116	−0.682	−1.319	−0.335	−1.705	−0.052	0.290	−1.801	0.147
T-14	−0.959	−0.167	0.979	−0.979	0.186	−1.132	−0.340	1.902	−1.170	0.378
T-15	−1.096	−0.104	0.613	−1.126	0.135	−0.991	0.000	−0.003	−0.990	−0.001
T-16	−0.899	0.180	−1.058	−0.809	−0.270	−0.864	0.216	−1.205	−0.839	−0.240

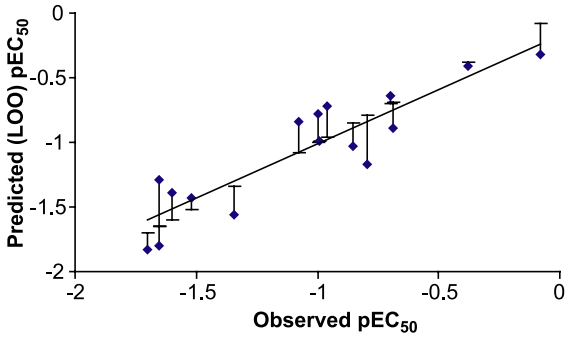


Figure 4. Plot between observed pEC_{50} and predicted (LOO) pEC_{50} with residual presentation for the training set using model 2.

Table 7. Observed and predicted pEC_{50} of the test set with residual using model 1 and model 2

Comp. No.	Observed pEC_{50}	Model 1		Model 2	
		Predicted pEC_{50}	Residual	Predicted pEC_{50}	Residual
Test-1	−1.708	−1.404	−0.304	−1.225	−0.483
Test-2	−1.415	−0.928	−0.487	−1.000	−0.415
Test-3	−0.301	−0.625	0.324	−0.488	0.187
Test-4	−0.763	−0.873	0.110	−0.484	−0.279
Test-5	−0.863	−0.644	−0.219	−0.835	−0.028
Test-6	−0.431	−0.730	0.299	−0.880	0.449
Test-7	−0.978	−1.141	0.163	−1.226	0.248

somewhat deviated from the β_3-adrenergic receptor agonist activity.

Model 2 has correlation coefficient on a par with model 1 ($r = 0.929$), but has moderately high correlation among the parameters with somewhat good internal consistency (Fig. 4 and Table 6), less predictive ability of the test set ($r^2_{pred} = 0.485$) than model 1 (Fig. 5 and Table 7). The linear contribution of each physiochemical parameters to the model shows somewhat low significance ($P < 0.03$) compared to model 1. Model 2 showed that E_ele and SlogP[15] contributed positively while SlogP_VSA8[15] contributed negatively. SlogP, which is Log of the octanol/water partition coefficient (including implicit hydrogens) and represents the lipophilic nature of the compound. This is essential for the transportation of the molecule to the active site and substitutions, which showed variation in SlogP value was related to the nature of the distal end group which may be hydrophobic or hydrophilic. This suggests that the hydrophobic character of the distal end moiety is essential for activity and probably interacts with a hydrophobic pocket in the receptor area. Thus, an increase in lipophilicity may increase agonist activity, which is also supported by model 1. SlogP_VSA8 contributed to the model to a very small extent. This is representative of the accessible van der Waals surface area of molecules with atom or atoms of bulkier nature.

Figure 5. Plot between observed pEC_{50} and predicted pEC_{50} with residual presentation for the test set using model 2.

Both models gave insight into some common important structural features. High electrostatic potential energy and the lipophilic nature of the molecule are favorable for the β_3-adrenergic receptor agonist activity. Thus, modification in structure to improve lipophilic character and electrostatic potential energy might result in a more potent β_3-adrenergic receptor agonist.

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