

# A QSAR analysis of some amino substituted Pyrido[3,2-b]pyrazinones as potent and selective PDE-5 inhibitors

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## Abstract

A QSAR study has been performed on a series of substituted pyrido[3,2-b]pyrazinones as potent and selective PDE-5 Inhibitors. The compounds in the selected series were characterized by spatial, molecular and electrotopological descriptors using QSAR module of molecular design suite (V-Life MDS<sup>TM</sup> 3.5). Correlations between inhibitory activities and calculated predictor variables were established through partial least square regression (stepwise forward) method. The generated QSAR models reveal that the topology of the molecules crucially influences the desired inhibitory activity of pyrido[3,2-b]pyrazinones. PDE-5 inhibition can be well defined by the models generated and the molecules are more selective towards PDE –5 while PDE –6 and PDE –11 inhibitory activities cannot be well delineated by the help of generated QSAR models. So PDE-5 selective compounds can be synthesized based on the assumption of the present QSAR analysis. The best model shows 90% correlation for PDE-5 inhibitory activity which explains good reliability of the model. However cross correlated regression coefficients ( $Q^2$ ) 0.5959 further validate the model significance. The present study imply that the PDE-5 inhibition can be augmented primarily by increasing molecular refractivity and number of carbons connected to the aromatic rings, single bonds and by decreasing number of carbons connected to the double bonds.

**Keywords:** Quantitative structure activity relationship (QSAR); molecular design suite (MDS); PDE-5 Inhibitors; pyrido[3,2-b]pyrazinones.

## Introduction

Phosphodiesterases (PDEs) are the enzymes which are responsible for the degradation of cyclic monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) that are imperative intracellular second messengers and play a vital role in regulating various cell functions.<sup>1</sup> Phosphodiesterase-5 (PDE-5) inhibitors have been proven to be effective for erectile dysfunction.<sup>2</sup> cGMP is a second messenger signaling molecule that is central to the regulation of many physiological processes, including smooth muscle tone (relaxes smooth muscles), visual transduction, platelet aggregation, bone growth, and electrolyte and fluid homeostasis.<sup>3</sup> Among the 11 different PDE families (PDE-1 to PDE-11) identified and characterized so far, cGMP-specific PDE-5, an isoenzyme is the primary target for the new drug development. PDE-5 is found in various tissues, most prominently the corpus cavernosum and the retina.<sup>4</sup> Research in PDE molecular targets has increased with the development of isozyme-selective PDE inhibitors that can produce potent inhibition of selected isozymes with fewer harmful effects compared to nonselective ones.<sup>5,6</sup> PDE-5 converts enzymatically the intracellular second messenger molecule cGMP to its inactive form. By its preservation, cGMP activates cGMP-dependent protein kinase I, which pivotally drives a biochemical cascade resulting in corporal smooth muscle relaxation and, hence, penile erection. This system mechanistically requires the synthesis of cGMP, secondary to the production and release of NO during sexual arousal. Accordingly, PDE-5 inhibitors augment the erectile response.<sup>7</sup> It was also found that selective increase in tumor capillary permeability appears to be mediated by a selective increase in tumor cGMP levels.<sup>8</sup> Sildenafil (Viagra) (**Figure 1**) is the first and only orally active PDE-5 inhibitor available for the treatment of ED.<sup>9,10</sup> An improved, second-generation PDE-5 inhibitor would be one with greater potency and specificity for PDE-5, resulting in an agent with potentially fewer PDE associated side effects and greater efficacy as a treatment for ED. Some other PDE-5 inhibitors are also known like Vardenafil-hydrochloride,<sup>11</sup> and FR226807<sup>12</sup> given in **Figure 1**.

In previous reports we have described the number of quinazolinones and their ability to inhibit Phosphodiesterases enzyme<sup>13,14</sup>. Along with potent PDE inhibitory activities, these compounds also showed a very promising anti-inflammatory activity<sup>15</sup>. Among the sixty two compounds, few compounds showed even more potent activities than the theophylline (**Figure 2**).

As part of our efforts in the field of PDE inhibitors, we turned our attention towards the development of selective PDE inhibitors with fewer side effects. Hence in this paper we report the QSAR analysis of some novel PDE-5 inhibitors.

## Results and Discussion

QSAR study of a series of amino substituted pyrido[3,2-b]pyrazinones was performed by using  $-\log$  of biological activity and various physiochemical descriptors as dependent and independent variable respectively and correlations were established using partial least square analysis. Among the models generated, the following model was selected on the basis of its statistical significance for further study.

### Model-1 for PDE-5

$$\text{BA} = -3.9773 + \text{SaasCE-index}[0.179236] + \text{SdssCE-index}[-2.62119] + \text{SsssCHE-index}[2.09548] + \text{Smr}[0.0887121].$$

$$r^2 = 0.8180, q^2 = 0.5959, F \text{ test} = 26.9660, r^2 \text{ se} = 0.4108, q^2 \text{ se} = 0.6121, \text{pred}_r^2 = 0.5545, \text{pred}_r^2 \text{se} = 0.5924.$$

The QSAR model 1 shows that all the molecules are selective for PDE-5 inhibition. The significant equation consists of four descriptors i.e. SaasCE-index, SdssCE-index, SsssCHE-index and Smr. The model expressed overall significance level better than 99%, as the calculated F value (26.9660) exceeds the tabulated ( $F = 3.83$ ) F value. The F-test reflects the ratio of the variance explained by the model and the variance due to the error in the regression. High value of the F-test indicates that the model is statistically significant. The squared correlation coefficient  $r^2$  (0.82) is a relative measure of quality of fit by regression equation. Correspondingly, it represents 82% variance in PDE-5 inhibitory activity exhibited by pyrido[3,2-b]pyrazinones. Its value is close to 1.0 which represents the better fit to the regression line. Standard deviation is measured by the error mean square, which expresses the variation of the residuals or the variation about the regression line. Thus standard deviation is an absolute measure of quality of fit and should have a low value for the regression to be significant. The leave-one-out procedure was used for internal validation of the model. In this procedure high

cross validated  $r^2$  ( $q^2= 0.60$ ), reflects the very good internal predictive power of the model. Another parameter for predictivity of test set compound is high  $\text{pred}_r^2 = 0.55$ , which show good external predictive power of the model. The results are listed in **Table 3** and the experimental versus predicted activity of both test set and training set are depicted in **Figure 2**. The inter-correlation among the selected descriptors was very less due to auto scaling and cross correlation limit permitted was 0.6, values of these selected descriptors are given in the **Table 4** and contribution chart of the selected descriptors are depicted in **Figure 3** Correlation matrix of the selected descriptors is given in the **Table 5** which shows good correlation of selected parameters with biological activity.

Out of four descriptors selected in the above mentioned model, three descriptor *viz.* SaasCE-index, SdssCE-index and SsssCHE-index are topological descriptors. These descriptors describe the overall topology of the molecules.

The SaasCE-index is an electrotopological state index for number of carbon atoms connected with one single bond along with two aromatic bonds. The positive correlation of the descriptor in the model indicates that electro-topological properties of the carbon atoms connected with aromatic rings and single bonds positively influences PDE-5 inhibitory activity shown by pyrido[3,2-b]pyrazinone derivatives.

The SdssCE-index an electro-topological parameter which can define the total number of carbon atoms connected with one double and two single bonds. The descriptor shows highest negative correlation among the parameters selected for the derived QSAR model. The negative coefficient suggests that inclusion of such carbon atoms in the molecules lead to decreased PDE-5 inhibition.

The highest positively contributed descriptor in the above mentioned model is SsssCHE-index, signifies total number of –CH groups connected with three single bonds. The positive correlation suggests that that PDE-5 inhibitory activity of pyrido[3,2-b]pyrazinone derivatives may be increased by increasing the number of such –CH groups present in the molecules. Further, it may be inferred that increasing the saturation of the aromatic rings will contribute to increased PDE-5 inhibition.

The last descriptor is Smr, signifies the molecular refractivity (including implicit hydrogen's). This property is an atomic contribution model that assumes the correct protonation state (washed structures). Its positive contribution suggests that the increment of the polarity of the molecule lead to increased PDE-5 inhibition, moreover it can also be said that more the number of polar groups in the molecule more will be the affinity of the molecules towards the PDE-5 inhibition.

### **Model-2 for PDE-6:**

$$BA = 5.9579 + SsssCHE\text{-index}[1.3263] + Ipc[0.0000] + SaaCHcount[-0.0603]$$

$$r^2 = 0.8209, q^2 = 0.6342, F \text{ test} = 29.7857, r^2 \text{ se} = 0.3280, q^2 \text{ se} = 0.4687, \text{pred\_}r^2 = 0.4688, \text{pred\_}r^2 \text{ se} = 0.5589.$$

The QSAR model 2 shows that all pyrido[3,2-b]pyrazinones derivatives are not selective towards PDE-6 Inhibition but only 24 compounds out of 30 are selective towards PDE-6 inhibition. The significant equation consists of three descriptors i.e. SsssCHE-index, Ipc and SaaCHcount. The model presented here explains 82% variance for PDE-6 inhibitory activity represented by pyrido[3,2-b]pyrazinone analogues. The leave-one-out procedure was used for internal validation of the model. In this procedure high cross validated  $r^2$  ( $q^2 = 0.63$ ) and low  $q^2\_se = 0.46$  value, reflects the very good internal predictive power of the model and is reasonable check for overfitting if the data.

The model demonstrates that the PDE-6 inhibition can be sufficiently explained by the three descriptors like SsssCHE-index, Ipc and SaaCHcount, contribution chart of the selected descriptors in the model-2 is presented in the **Figure 4**.

SsssCHE is a topological index, signifies total number of -CH groups connected with three single bonds. A high positive correlation suggests that better PDE-6 inhibition can be achieved by increasing the saturated rings and saturated aliphatic chains. The SaaCHcount descriptor signifies the total number of carbon atoms connected with a hydrogen atom along with two aromatic rings, its negative coefficient value take to a mean that confiscation of such groups will resulting in better affinity towards the PDE-6 inhibition. Information theory based descriptor

(Ipc) is positively contributing to the activity but the value does not contribute or effects the PDE-6 inhibition.

Values of all the descriptors selected in the model-2 are given in the **Table 6** and Correlation matrix of the selected descriptors is given in the **Table 6**. Predicted and actual activity values are given in **Table 3**.

### **Model 3 PDE-11**

It was not possible to obtain any significant model for PDE-11 activity, the derived models were not able to explain the PDE-11 inhibition and therefore the model is not presented here for the explanation.

## **Conclusions**

The QSAR study presented here is satisfactory in terms of statistical significance and is explanatory in terms of descriptors selected. The model described above demonstrate that the overall PDE-5 inhibition can be achieved by increasing the saturated alkyl or aryl chain length, in other sense the overall lipophilicity can be increased up to a suitable extent. Better PDE-5 inhibition can also be achieved by increasing the number of carbons connected with aromatic rings and single bonds. The study also suggests that elimination of carbons connected with double bonds will provide potent compounds towards PDE-5 inhibition. The overall polarizability of the molecules is also essential for the activity and binding to the receptor but it is not useful for improvement of PDE-6 inhibition. While the removal of total number of carbon atoms connected with a hydrogen atom along with two aromatic rings can increase PDE-6 inhibition. The study also reveals that total number of –CH groups connected with three single bonds are important for both PDE-5 and PDE-6 inhibition and improvement of such groups will provide nonselective PDE inhibitors. Thus one can change polarity of the molecule for generating PDE-5 selective compounds. The findings of the study will be helpful in the design of the potent and selective PDE-5 inhibitors which will be potent compounds of clinical utility.

## **Experimental Section**

The QSAR studies were performed on a series of amino substituted pyrido[3,2-b]pyrazinones as potent and selective PDE-5 inhibitors reported by Dafydd R. Owen *et al.*<sup>16</sup> The selected series shows three types of inhibitory activities *viz.* inhibition of PDE-5, PDE-6 and PDE-11. The dataset consist of total of 30 compounds. Of the total dataset of the compounds, **30**, **24** and **22** compounds bear well defined activities for PDE-5, PDE-6 and PDE-11 respectively.

For correlation purposes, reported IC<sub>50</sub> values were converted to their molar units and subsequently to free energy related negative logarithmic state, i.e.  $-\log(1/IC_{50})$ . The compounds along with their pIC<sub>50</sub> are summarized in **Table 1**.

### **Computer software**

Each compound was energy minimized and batch optimized by using Merck Molecular Force Field (MMFF) fixing Root Mean Square Gradients (RMS) to 0.01 Kcal/mol Å. The optimized batch of molecules was selected for calculation of the physiochemical descriptors. 2D molecular descriptors are defined to be numerical properties that can be calculated from the connection table representation of a molecule (e.g., elements, formal charges and bonds, but not atomic coordinates). 2D descriptors<sup>17</sup> are, therefore, not dependent on the conformation of the molecule and are most suitable for large database studies. The descriptor pool was reduced by eliminating out the descriptors with constant and near constant values. Further reduction in the descriptor pool was done by ousting the descriptors that are highly degenerate and difficult to interpret. A correlation analysis was performed between biological data and remaining descriptors, most of which were molecular and electro-topological descriptors and the descriptors those were showing very low correlation with inhibitory activity were also removed. Remaining descriptor pool was then used for generating QSAR models. The descriptors selected for modeling inhibitory activity of the piperazinyl phenylalanine derivatives are summarized in **Table 2**.

The random selection method was used for training data selection at 73% and 66% for PDE-5, and PDE-6 inhibition respectively. Variable selection was performed by simulated annealing method. The QSAR model was generated by using partial least square (PLS) method by using V-Life Molecular Design Suite (MDS). The program computes the best model on the basis of squared correlation coefficient  $r^2$ , cross validated  $q^2$ , F-test and predicted  $-r^2$ . The calculated value of F-test when compared with tabulated value of F-test shows the level of statistical significance (99.99%) of the QSAR model. The low standard error of pred\_ $r^2$ \_se,  $q^2$ \_se and  $r^2$ \_se shows absolute quality of fitness of the model. The correlation matrix was developed by using SYSTAT-11.<sup>18</sup>

The generated QSAR models were validated for predictive ability inside the model by using cross validation (Jack-Knife method or leave one out) for  $q^2$  and external validation, which is more robust alternative method by dividing the data into training set and test set and

calculating  $\text{pred}_r^2$ . The high  $\text{pred}_r^2$  and low  $\text{pred}_r^2\text{se}$  were show high predictive ability of the model.

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## FIGURE CAPTIONS

**Figure 1.** PDE-5 Inhibitors

**Figure 2.** Previously synthesized compounds by our lab having PDE inhibitory.

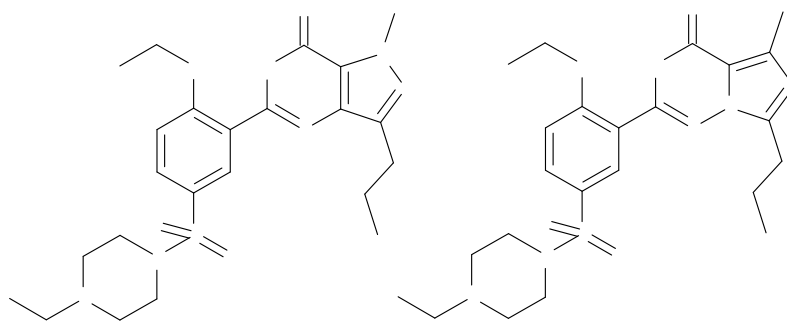
**Figure 3.** Graphical plot between observed and predicted activity values of training and test set compounds in QSAR model-1 against PDE-5..

**Figure 4.** Contribution chart of the selected descriptors in the model-1.

**Figure 5.** Contribution chart of the selected descriptors in the model-2

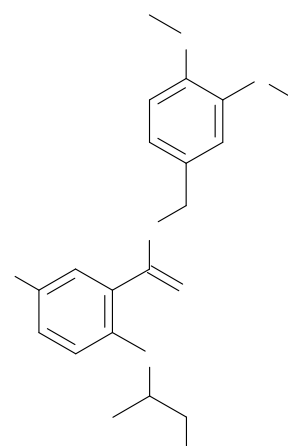
**Figure 6.** Graphical Plot between observed versus predicted activity values for training and test set compounds for PDE-6 inhibition

**Figure 1. PDE-5 Inhibitors.**



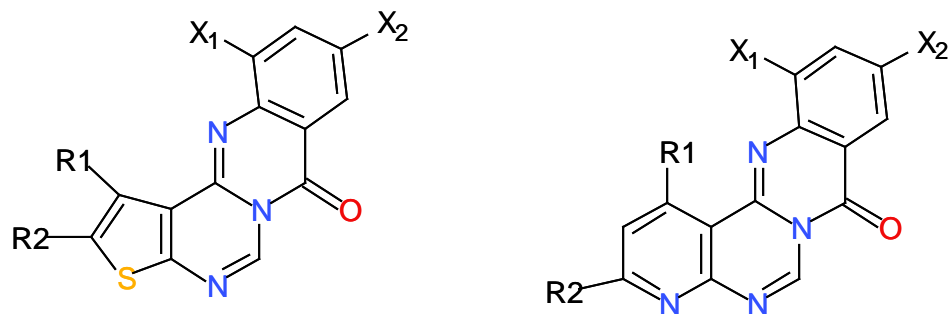
**Sildenafil**

**Verdenafil**

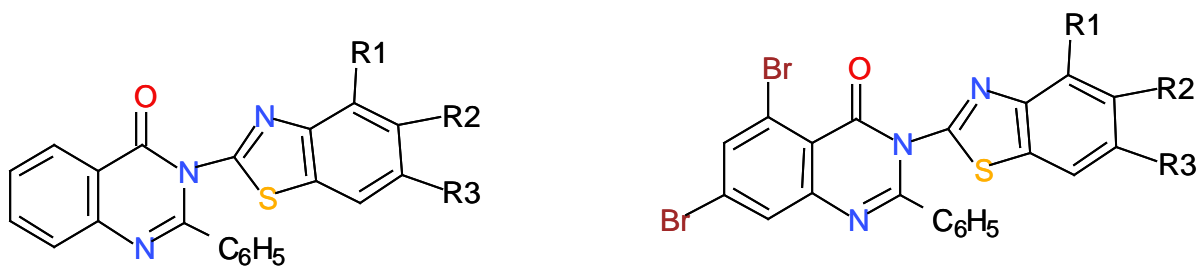


**FR 226807**

**Figure 2.** Previously synthesized compounds by our lab having PDE inhibitory.

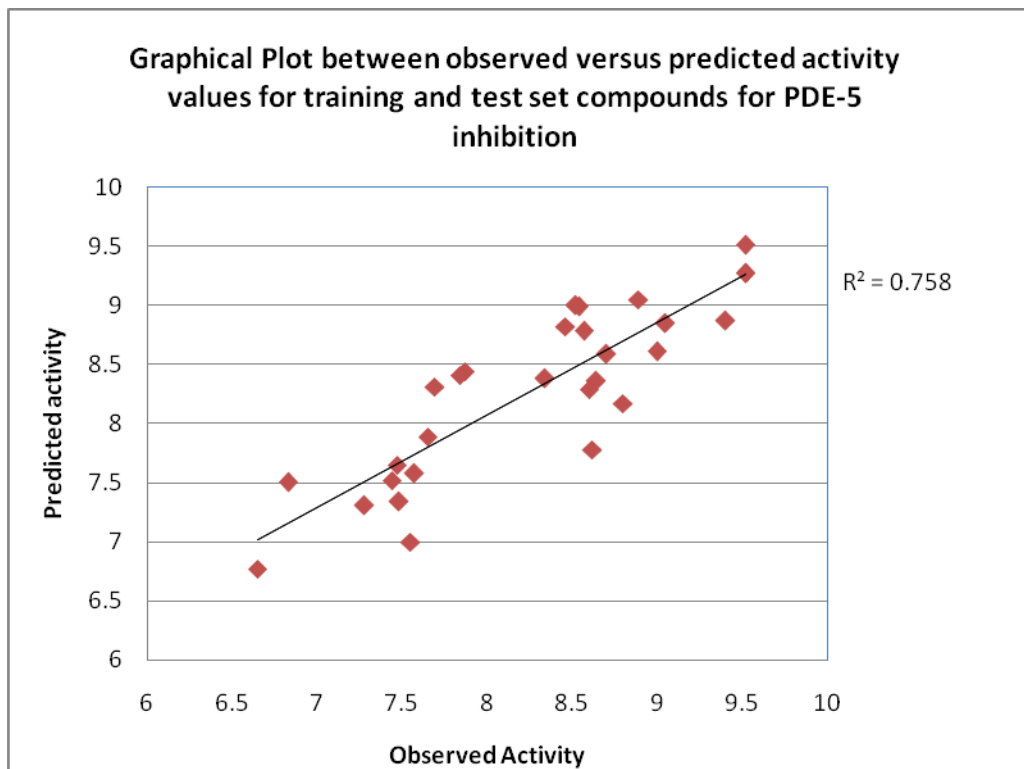


Where R1 and R2 = H, Alkyl and Aryl; X1 & X2 = H or Br

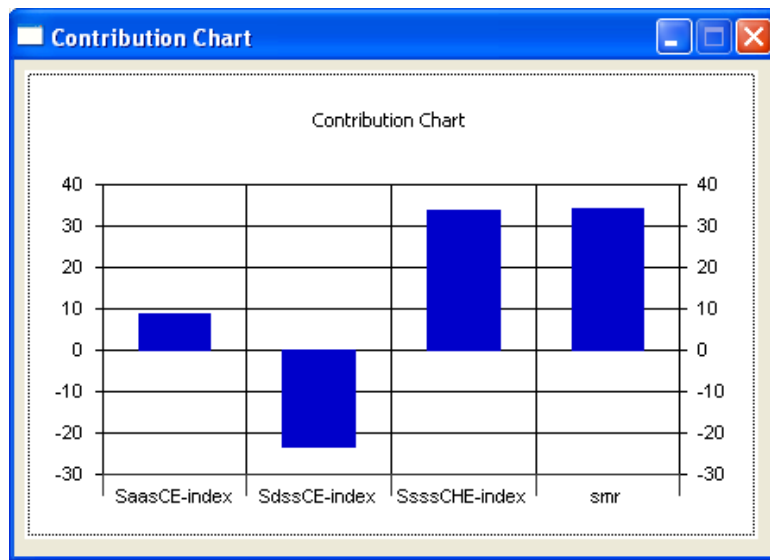


Where R1, R2, and R3 = H, CH<sub>3</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, Cl, Br and NO<sub>2</sub>

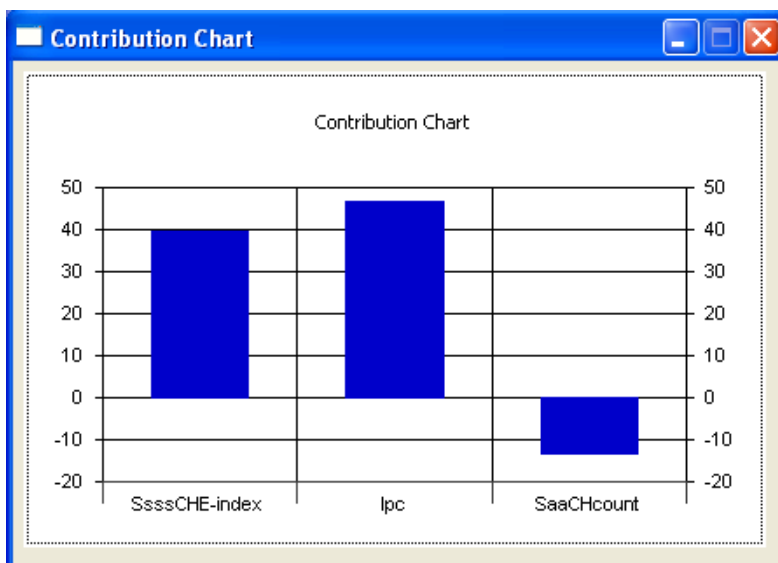
**Figure 3.** Graphical plot between observed and predicted activity values of training and test set compounds in QSAR model-1 against PDE-5.



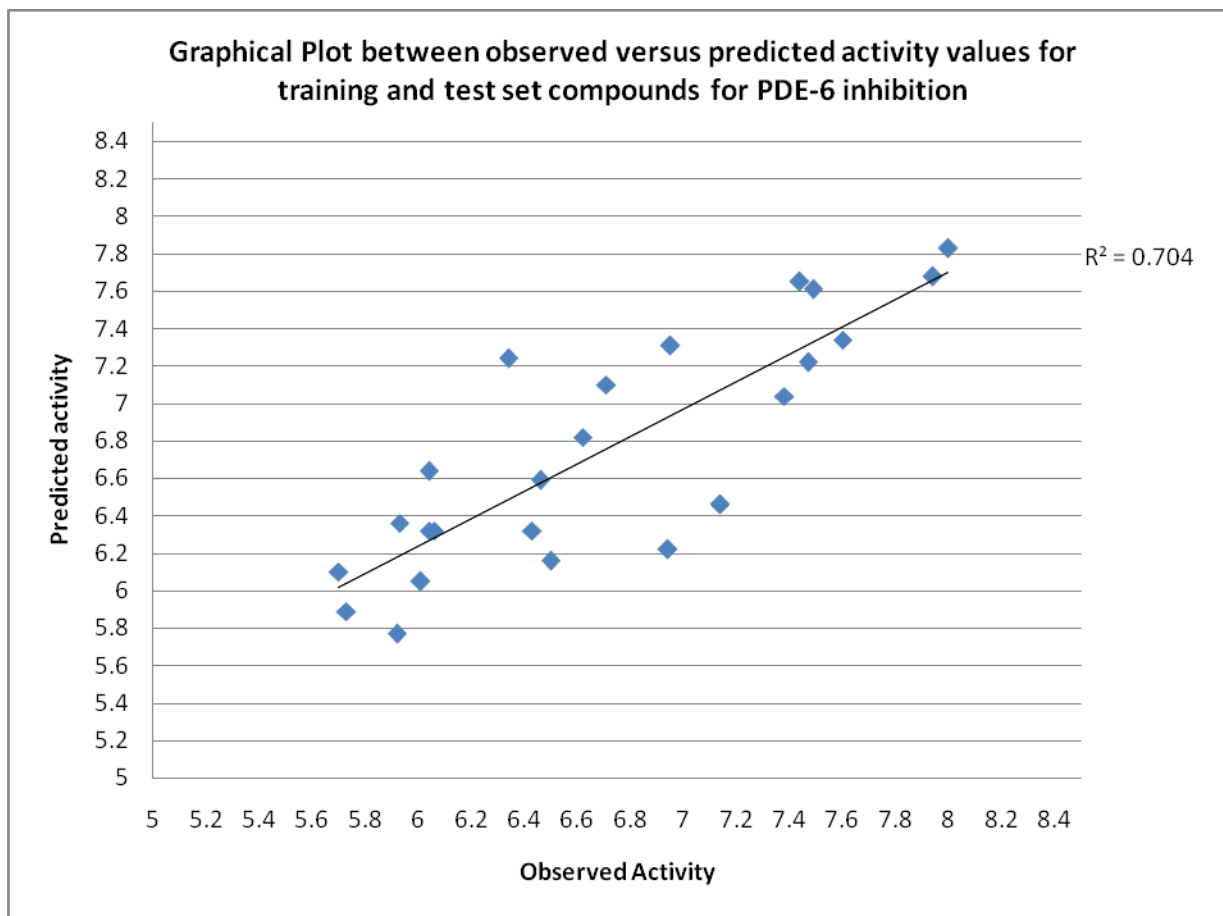
**Figure 4.** Contribution chart of the selected descriptors in the model-1



**Figure 5.** Contribution chart of the selected descriptors in the model-2



**Figure 6.** Graphical Plot between observed versus predicted activity values for training and test set compounds for PDE-6 inhibition





## **TABLES.**

**Table 1** Structures of the compounds of the selected series with their inhibition data.

**Table 2** Classification of descriptors of molecular design suite.

**Table 3** Observed and predicted activity values of training and test set compounds in QSAR model-1 and model-2 against PDE-5 and PDE-6 respectively.

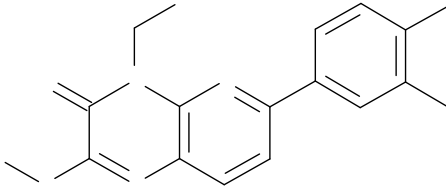
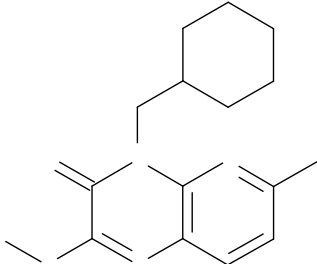
**Table 4** Values of the selected descriptors for QSAR model 1 PDE-5 inhibition.

**Table 5** Pearson Correlation matrix of the selected descriptors in the model-1

**Table 6** Values of the selected descriptors for QSAR model-2 against PDE-6 inhibition.

**Table 7** Pearson Correlation matrix of the selected descriptors in the model-2

**Table 1** Structures of the compounds of the selected series with their inhibition data.

Comp. code	R1	R2	X	- Log IC <sub>50</sub>		
				PDE-5	PDE-6	PDE-11
						
9	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-CH <sub>2</sub> CH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> ON	H	8.89	8.00	6.46
10	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-CH <sub>2</sub> CH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> ON	F	8.70	7.94	6.32
11	- C <sub>5</sub> H <sub>4</sub> N	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	H	8.60	6.43	6.32
12	- C <sub>5</sub> H <sub>4</sub> N	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	H	7.69	6.04	6.01
13	-3,5 di F C <sub>6</sub> H <sub>3</sub>	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	H	8.57	6.04	6.41
14	-C <sub>6</sub> H <sub>5</sub>	H	H	7.55	6.94	6.84
15	-C <sub>6</sub> H <sub>5</sub>	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	H	8.52	6.34	6.49
16	-C <sub>6</sub> H <sub>5</sub>	4-CH <sub>2</sub> CH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> ON	H	8.34	6.62	6.39
17	-C <sub>6</sub> H <sub>11</sub>	4-CH <sub>2</sub> CH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> ON	F	8.80	6.71	6.67
18	-C <sub>6</sub> H <sub>5</sub>	3-CH <sub>2</sub> C <sub>5</sub> H <sub>4</sub> N	H	7.87	6.06	6.25
19	-C <sub>6</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>2</sub> N-COCH <sub>2</sub> -	H	8.46	NA	7.04
20	-CH <sub>2</sub> O-CH (CH <sub>3</sub> ) <sub>2</sub>	4-CH <sub>2</sub> CH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> ON	F	7.28	6.01	5.78
21	-CH <sub>2</sub> O-CH <sub>2</sub> CH <sub>3</sub>	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	H	6.83	NA	NA
22	-CH <sub>2</sub> O-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	H	7.65	NA	NA
23	-CH <sub>2</sub> O-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	4-CH <sub>2</sub> CH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> ON	H	7.48	5.73	NA
24	-CH( CH <sub>3</sub> ) <sub>2</sub>	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	H	6.65	NA	NA
						
Comp. code	R2	Ar	- Log IC <sub>50</sub>			
			PDE-5	PDE-6	PDE-11	
25	4-CH <sub>2</sub> CH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> ON	3,5 (CH <sub>3</sub> ) <sub>2</sub> C <sub>3</sub> NO	9.00	7.38	6.54	

26	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	4 -C <sub>5</sub> H <sub>4</sub> N	9.05	7.47	7.44
27	(CH <sub>3</sub> ) <sub>2</sub> N-COCH <sub>2</sub> -	2-OCH <sub>3</sub> - C <sub>5</sub> H <sub>3</sub> N	9.52	7.14	8.11
28	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	2-OCH <sub>3</sub> - C <sub>5</sub> H <sub>3</sub> N	9.52	7.49	8.09
29	4-CH <sub>2</sub> CH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> ON	2-OCH <sub>3</sub> - C <sub>5</sub> H <sub>3</sub> N	9.40	7.60	8.23
30	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	2-OCH <sub>3</sub> - C <sub>4</sub> H <sub>2</sub> N <sub>2</sub>	9.52	7.44	8.09
31	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	2-OH - C <sub>5</sub> H <sub>3</sub> N	8.54	6.95	7.10
32	4-CH <sub>2</sub> CH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> ON	3,5 (CH <sub>3</sub> ) <sub>2</sub> C <sub>3</sub> NO	7.44	5.70	NA
33	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	- C <sub>5</sub> H <sub>4</sub> N	7.47	5.93	NA
34	(CH <sub>3</sub> ) <sub>2</sub> N-COCH <sub>2</sub> -	2-OCH <sub>3</sub> - C <sub>5</sub> H <sub>3</sub> N	7.84	5.92	5.92
35	4-CH <sub>2</sub> C <sub>5</sub> H <sub>9</sub> O	2-OCH <sub>3</sub> - C <sub>5</sub> H <sub>3</sub> N	8.64	6.46	5.91
36	4-CH <sub>2</sub> CH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> ON	2-OCH <sub>3</sub> - C <sub>5</sub> H <sub>3</sub> N	8.62	6.50	5.81
37	4-CH <sub>2</sub> CH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> ON	2-OCH <sub>3</sub> - C <sub>4</sub> H <sub>2</sub> N <sub>2</sub>	7.57	NA	NA
38	4-CH <sub>2</sub> CH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> ON	2-OH - C <sub>5</sub> H <sub>3</sub> N	6.27	NA	NA

\*PDE isoforms inhibition -log IC<sub>50</sub> values (in molar units)

**Table 2** Classification of descriptors of molecular design suite.

<b>Sr. No.</b>	<b>Type</b>	<b>Descriptor</b>
1	Spatial	Individual
2	Molecular	Chi, ChiV, Path count, Chi Chain, ChiV Chain, Chain path count, Cluster, Path cluster, Kappa, ElementCount, Polar surface area
3	Electro-topological	Estate number
4	Electro-topological	Estate contribution

**Table 3** Observed and predicted activity values of training and test set compounds in QSAR model-1 and model-2 against PDE-5 and PDE-6 respectively.

For PDE-5				For PDE-6			
Compounds code	Observed activity	Predicted activity	Residual activity	Compounds code	Observed activity	Predicted activity	Residual activity
<b>Training Set Compounds</b>							
<b>10</b>	8.70	8.59	0.11	<b>18</b>	6.06	6.32	-0.26
<b>29</b>	9.40	8.87	0.53	<b>11</b>	6.43	6.32	0.11
<b>37</b>	7.57	7.58	0.00	<b>28</b>	7.49	7.61	-0.12
<b>24</b>	6.65	6.77	-0.12	<b>12</b>	6.04	6.32	-0.28
<b>16</b>	8.34	8.38	-0.05	<b>25</b>	7.38	7.04	0.34
<b>21</b>	6.83	7.50	-0.67	<b>31</b>	6.95	7.31	-0.36
<b>26</b>	9.05	8.85	0.19	<b>34</b>	5.92	5.77	0.15
<b>30</b>	9.52	9.27	0.26	<b>35</b>	6.46	6.59	-0.13
<b>36</b>	8.62	7.78	0.83	<b>14</b>	6.94	6.22	0.73
<b>20</b>	7.28	7.31	-0.03	<b>9</b>	8.00	7.83	0.17
<b>27</b>	9.52	9.27	0.25	<b>32</b>	5.70	6.10	-0.40
<b>31</b>	8.54	8.99	-0.45	<b>29</b>	7.60	7.34	0.26
<b>9</b>	8.89	9.05	-0.16	<b>30</b>	7.44	7.65	-0.21
<b>35</b>	8.64	8.36	0.28	<b>20</b>	6.01	6.05	-0.04
<b>28</b>	9.52	9.51	0.01	<b>16</b>	6.62	6.82	-0.20
<b>13</b>	8.57	8.78	-0.21	<b>26</b>	7.47	7.22	0.26
<b>12</b>	7.69	8.31	-0.62				
<b>32</b>	7.44	7.52	-0.08				
<b>33</b>	7.47	7.65	-0.18				
<b>14</b>	7.55	7.00	0.55				
<b>23</b>	7.48	7.34	0.14				
<b>18</b>	7.87	8.44	-0.57				
<b>Test Set Compounds</b>							
<b>11</b>	8.60	8.29	0.31	<b>10</b>	7.94	7.68	0.25
<b>15</b>	8.52	9.00	-0.48	<b>13</b>	6.04	6.64	-0.59
<b>17</b>	8.80	8.17	0.62	<b>15</b>	6.34	7.24	-0.91
<b>19</b>	8.46	8.82	-0.36	<b>17</b>	6.71	7.10	-0.39
<b>22</b>	7.65	7.89	-0.24	<b>23</b>	5.73	5.89	-0.16
<b>25</b>	9.00	8.61	0.39	<b>27</b>	7.14	6.46	0.68
<b>34</b>	7.84	8.41	-0.57	<b>33</b>	5.93	6.36	-0.43
<b>38</b>	6.27	7.31	-1.04	<b>36</b>	6.50	6.16	0.34

**Table 4** Values of the selected descriptors for QSAR model 1 PDE-5 inhibition.

S. No.	SaasCE-index	SdssCE-index	SsssCHE-index	Smr
9	3.8	0.1	0.0	141.1
10	1.3	-0.1	0.0	136.4
11	3.1	0.1	0.4	124.0
12	2.9	0.1	0.4	124.0
13	0.3	-0.3	0.4	126.1
14	2.3	-0.3	0.5	99.8
15	2.5	0.3	1.0	127.2
16	2.5	0.3	0.5	130.9
17	0.2	0.1	0.4	130.9
18	3.4	0.2	0.4	127.0
19	2.2	-0.3	0.4	122.4
20	-0.2	-0.1	0.0	125.4
21	2.2	0.1	0.5	117.1
22	2.2	0.1	0.5	121.7
23	2.2	0.1	0.0	125.5
24	2.3	0.1	0.3	114.3
25	4.5	0.3	0.5	130.5
26	3.3	0.4	1.0	125.0
27	3.2	-0.2	0.4	126.7
28	3.6	0.3	1.0	131.6
29	3.5	0.3	0.5	135.3
30	3.1	0.3	1.0	129.4
31	2.8	0.3	1.0	126.7
32	4.2	0.1	0.0	125.0
33	3.0	0.2	0.5	119.6
34	2.9	-0.4	0.0	121.3
35	3.3	0.2	0.5	126.1
36	3.2	0.1	0.0	129.8
37	2.8	0.1	0.0	127.6
38	2.4	0.1	0.0	125.0

**Table 5** Pearson Correlation matrix of the selected descriptors in the model-1

<b>Descriptors</b>	<b>SaasCE-index</b>	<b>SdssCE-index</b>	<b>SsssCHE-index</b>	<b>Smr</b>
<b>SaasCE-index</b>	1.000			
<b>SdssCE-index</b>	0.414	1.000		
<b>SsssCHE-index</b>	0.196	0.528	1.000	
<b>Smr</b>	0.145	0.365	-0.047	1.000

**Table 6** Values of the selected descriptors for QSAR model-2 against PDE-6 inhibition.

S. No.	SsssCHE-index	Ipc	SaaCH count
1.	0	2.49E+08	10
2.	0	2.28E+08	9
3.	0.445738	37628787	10
4.	0.443393	37628787	10
5.	0.352212	75883261	9
6.	0.460859	920098.3	6
7.	0.961194	37628787	6
8.	0.467155	61137360	6
9.	0.404603	91402281	5
10.	0.448612	37628787	10
11.	0.014474	37216593	5
12.	0	29453595	6
13.	0.488676	55988604	2
14.	1.029081	25750359	6
15.	0.422608	24448501	5
16.	0.99446	64268021	5
17.	0.48737	1.04E+08	5
18.	0.97517	64268021	4
19.	0.968636	37628787	5
20.	0	26952765	2
21.	0.485348	12397264	6
22.	0	11771442	5
23.	0.472275	30961218	5
24.	0	50296565	5



**Table 7** Pearson Correlation matrix of the selected descriptors in the model-2

<b>DESCRIPTORS</b>	<b>SSSCHEINDE</b>	<b>IPC</b>	<b>SAACHCOUNT</b>
<b>SSSCHEINDE</b>	1.000		
<b>IPC</b>	-0.282	1.000	
<b>SAACHCOUNT</b>	-0.134	0.390	1.000