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2D QSAR ANALYSIS ON SUBSTITUTED PYRROLIDINE DERIVATIVES AS DIPEPTIDYL PEPTIDASE –IV INHIBITORS

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ABSTRACT
Computational methodology, QSAR was applied in order to achieve best 2D QSAR models. The whole 2D QSAR study was performed on a series of substituted pyrrolidine derivatives with a sum of total forty synthesized molecules as dipeptidyl peptidase IV blocking agents. TheQsar studies were done by the aid of software named as VLifeMDS. All the forty molecules were considered as data set which were further divided into training set and test set by the help of random selection method associated with stepwise forward backward method. Partial least square regression analysis was done and the best models were identified in terms of r^2 (squared correlation coefficient) and q^2 (cross validatedcorrelation coefficient) values. Three best models were identified with r^2values of 0.7681, 0.7352, 0.7264and q^2 values with 0.5193, 0.6037, 0.5626 for model 1, 2 and 3 respectively. Different descriptors and their contribution in building two dimensional QSAR models reveals that the generated models were good for predicting dipeptidyl peptidase IV inhibitory activity.

Keywords: Diabetes, Pyrrolidine, QSAR, Dipeptidyl peptidase IV, Partial least square regression.

INTRODUCTION

Diabetes is a major disorder facing by persons worldwide. A person suffering from diabetes is more prone to other diseases as compared to non-diabetic person It was projected that around 300 million peoples are going to be come under diabetic condition by the year 2025[1]. Diabetes is categorized into type 1(Insulin dependent) and type 2 (Non-insulin dependent) diabetes in which type 2 diabetes is more in people due to their sedentary lifestyle habits. As the level of glucose increases in the blood it will hamper other vital organs in the body such as heart ,kidneys and eyes resulting in failure of kidneys, heart and glaucoma[2]

Diabetes treatment still remains a challenge. For management of type -2 diabetes, there are few new classes of agents has been successfully discovered besides existing treatment. The agents are targeted towards Incretins and Dipeptidyl Peptidase-IV. In the year 1980 the role of GLP-1 came to knowledge as a potent stimulant of insulin release[3].Incretins such as, GIP (glucose-dependent insulinotropic polypeptide), GLP-1(glucagons like peptide) stimulate insulin secretion in presence of glucose load. Patients with type-2 diabetes generally lack the glucose-lowering response to GIP. In contrast, the insulinotropic response to GLP-1 is typically intact in this patient population, but circulating levels of postprandial GLP-1 is deficient.The activity of incretins depends on the enzyme dipeptidyl peptidase IV. As the dipetidyl peptidase IV enzyme was blocked, the secretion of insulin was regulated by the help of incretins and controls the blood glucose level. Therefore it is important to inhibit dipeptidyl peptidase IV enzyme for smooth regulation of insulin in the body[4,5].

Two dimensional quantitative structure activity relationship is a method which does not consider the molecule as a whole. Models of 2D-QSAR analysis help to determine the relationship of biological activity with selected physicochemical properties. Properties like bond angles, bond distances are not taken into consideration in this method. In 2D-QSAR descriptors are empirically determined, which many times fail to separate two properties influencing a particular reaction. As 2D-QSAR is a practical approach, it is

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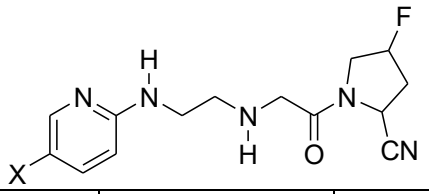
performed in the beginning. It helps to determine whether the data set chosen capable of producing a good model or not [6, 7].

Substituted cyano pyrrolidine derivatives has been reported as DPP-IV enzyme inhibitors [8, 9]. In present study, an attempt has been made to build new models which shown promising result to develop new molecules of substituted cyano pyrrolidine derivatives for the treatment of diabetes by the aid of 2D QSAR. A series of 40 substituted cyano pyrrolidine molecules has been selected for establishing QSAR models [10].

MATERIALS AND METHODS.

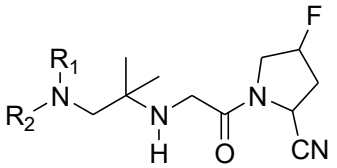
To develop QSAR models, data set of molecules were required. In this research, forty molecules were considered as data set. The structure of the forty molecules were shown in Table 1, 2 and 3.In QSAR study, the reported IC_{50} values has been converted into pIC_{50} values [11].All QSAR operations were done with the help of VLifeMDS software [12].

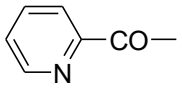
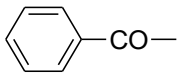
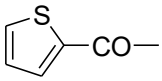
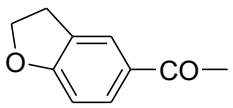
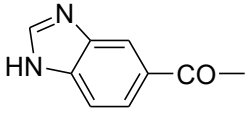
Table-1: Common structure of the compounds of 4-fluoro-2-cyanopyrrolidine derivatives and their biotic actions



S.NO	MOLECULE	X	IC_{50} (NM)	$log(1/IC_{50})$
01	2a	CN	1.1	8.959
02	2b	H	2.8	8.553
03	2c	Cl	2.7	8.569
04	2d	$CONH_2$	2.4	8.62

Table -2: Common structure of 4-fluoro-2-cyanopyrrolidine derivatives and their biotic actions.



S.NO	MOLECULE	R_1	R_2	IC_{50} (nM)	$log(1/IC_{50})$
5	10a		H	8.2	8.086
6	10b		H	4.5	8.347
7	10c		H	5.4	8.268
8	10d		H	2.9	8.538
9	10e		H	5.7	8.244

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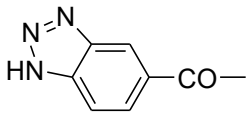
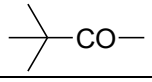
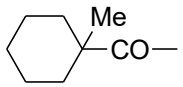
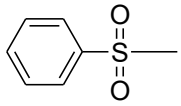
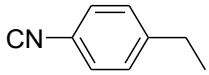
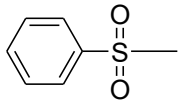
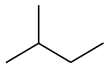
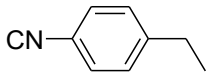
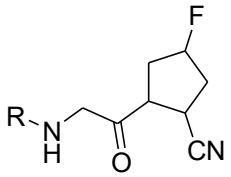
10	10f		H	1.5	8.824
11	10g		H	5.8	8.237
12	10h		H	13	7.886
13	10i	(4-Cl-Ph)$_2$CHCO-	H	106	6.963
14	10j		H	75	7.125
15	10l		H	39	7.409
16	11a		Me	31	7.509
17	11b	Et	Et	252	6.599
18	11c		PhCO-	7.3	8.137
19	11d		PhCO-	6.2	8.208

Table - 3: Common structure of the compounds of 4-fluoro-2-cyanopyrrolidine derivatives and their biotic actions.



S.NO	MOLECULE	R	IC_{50} (nM)	$log(1/IC_{50})$

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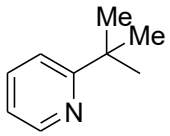
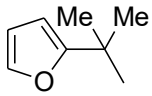
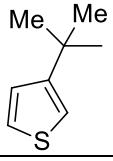
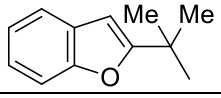
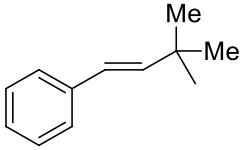
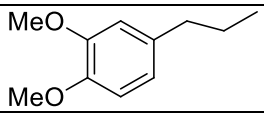
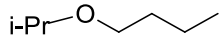
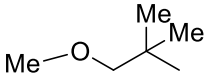
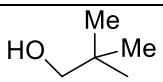
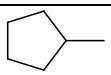
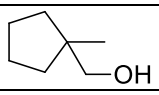
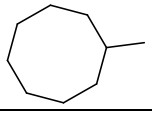
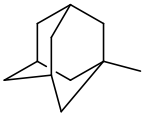
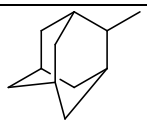
20	12a		22	7.658
21	12b		8.6	8.066
22	12c		12	7.921
23	12d		88	7.056
24	12e		16	7.796
25	12f		27	7.569
26	12g	t-Bu-	2.9	8.538
27	12h	i-Pr-	7.8	8.108
28	12i		8.7	8.06
29	12j		13	7.886
30	12k		4.6	8.337
31	12m		33	7.481
32	12n		3.1	8.509
33	12o		2.6	8.585
34	12p		3.3	8.481
35	12q		3.3	8.481
36	12r		4.1	8.387
37	12s		3.1	8.509

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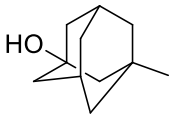
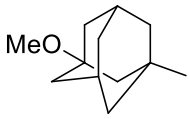
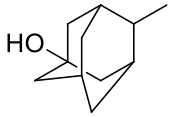
38	12t		3.1	8.509
39	12u		8.3	8.081
40	12v		5.3	8.276

Modeling of molecules:
The overall QSAR work has been performed on computer system and the details are as,

Device Name	HP
Processor	**Intel (R) core(TM) i3-6006U CPU@ 2.00GHz**
RAM	**4GB**
System type	**64 bit operating system, x64-based processor**
Edition	**Windows 10 pro**
Version	**1903**
Installed QSAR Software	**VLifeMDS 4.6**

First of all, the structures of 40 molecules were drawn with the aid of "draw 2d structure" application which was present in the VLifeMDS software. Once when all the structures were drawn completely then the next step was to minimize the energy of 2D structures. Energy minimization was done by the help of MMFF with maximum number of cycles, root mean square gradient and dielectric constant, were in the range of 10000, 0.01 and 1.0 respectively. Next was to select the electrostatic and steric energy cutoff which was in the range of 20 and 10 kcal/mol.

DESCRIPTORS INVOLVED IN 2D QSAR:
Descriptors plays an important role for the development of Qsarmodels. Descriptors were categorized into three types. The first descriptor was selected as physicochemical descriptors which included total fourteen descriptors category such as individual, Chi, ChiV, Path ,Chain path and Element count, Chi and chiV chain, Cluster and Path cluster, Kappa, Estate numbers, Estate contributions, Polar surface area. The selection of second type descriptor was alignment independent descriptors in which different attributes were used to calculate more than two hundred descriptors.The different attributes used for the calculation of descriptors were T_2_O_7, T_2_N_5, T_2_2_6, T_C_O_1 etc. The next step in alignment independent descriptors was the selection of structural descriptors which was selected as topological with minimum and maximum range of 0 to 7 followed by selecting 2, 3,T(any) C, N, O ,F ,Cl, S as attributes. The third type descriptor selected as atom type count descriptors which was based on merck molecular force field (MMFF)

BUILDING DATA OF TRAINING AND TEST SETS:
When calculation for descriptors were done, a work sheet was obtained in which all the selected descriptors values were shown. The generated worksheet was saved in .qsr file format for further calculation. The next step was the selection of training and test set of the respective series of 40 molecules. For generation of test and training set of all the molecules were subjected to different selection methods like manual, random, sphere exclusion etc. In present work, Random selection method was applied for the generation of test and training set. Different random trails has been done to distinguish training and test set in terms of various percentages like 70%, 75%, 80% etc. 10-15 trials were run in each random selection to evaluate the QSAR

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models based on selected training and test set molecules. When the training and test set were confirmed then selection of regression method was done as Partial least quare method followed by stepwise forward backward method. The criteria selected for stepwise forward backward method was 0.5 for cross correlation limit, variable number at one fifth of training set sum, r2 as selection term, F-test values at 4 for In and for out it was 3.99, also cross validation was selected for model building.

PARTIAL LEAST SQUARE REGRESSION (PLS):

In the field of Pharmaceutical chemistry, Applied chemistry, Economics, Management and even in Psychology, PLS has been widely used because of its simplest form which is based on linear relationship between the dependent variables and independent variables. In present study, PLS was applied to build QSAR models. Partial least square regression analysis is an advanced method over multiple linear regression (MLR) method. Prediction functions were represented by factors which was extracted from the matrix Y`XX`Y. Partial least square regression method is undoubtedly the minimum obstructive of the different multivariate extensions of methods such as MLR. In PLS regression analysis the calculated descriptors were considered as independent while that of biotic action were used as dependent variable in order to achieve linear regression.

RESULT AND DISCUSSION:

In present research work, development of 2d QSAR models were achieved by means of regression analysis named as partial least square regression method coupled with stepwise forward backward method. A series consisting of forty substituted pyrrolidine derivatives were selected to accomplish the whole QSAR study. The forty data set of derivatives were separated randomly into training and test set in order to build best 2D QSAR models with different trials. Training and test set were selected if they follow the Unicolumn statistics(Table-4). This result shows that the test is interpolative i.e., derived from the min-max range of training set. The mean and standard deviation of the training and test set provides insight to the relative difference of mean and point density distribution of the two sets.

Table 4. Unicolumn statistics for different models

Model no.	Column name	Average	Maximum	Minimun	StdDev	Sum
MODEL 1	Training Set	8.0367	8.8240	6.5990	0.5593	257.1740
	Test set	8.2751	8.9590	7.5690	0.3966	66.2010
MODEL 2	Training Set	8.0402	8.8240	6.9630	0.5042	217.0850
	Test set	8.1762	8.9590	6.5990	0.6050	106.2900
MODEL 3	Training Set	8.0482	8.9590	6.5990	0.5320	257.5410
	Test set	8.2293	8.6200	6.9630	0.5579	65.8340

Result of best three 2D QSAR models by PLS regression analysis was shown in Table 5. The 2D QSAR statistically significant models with different test set molecules was shown in Table 6.

Table 5: Result of PLS regression method using Random selection

BEST MODEL	RANDOM %	TRIAL No.	TEST SET	PLS					
				r^2	q^2	pred_r^2	r^2se	q^2se	pred_r^2se
MODEL 1	80%	03	2a,2b,10b, 10c,10g,11d, 12f,12i.	0.7681	0.5193	0.4733	0.2834	0.4081	0.3421

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MODEL 2	70%	06	2a,2c,2d, 10a,10d,11a, 11b,12b,12c, 12o,12q,12v, 12u	0.7352	0.6037	0.0268	0.2700	0.3304	0.6129
MODEL 3	80%	08	2c,2d,10i,12 b,12g,12i,12 n,12s	0.7264	0.5626	0.6621	0.2928	0.3703	0.3433

Table 6: Statistical significant models.

MODEL	TRIAL No	TEST SET MOLECULES	EQUATION
Model 1	**03**	2a,2b,10b, 10c,10g,11d, 12f,12i.	SssCH2count -0.6682 RotatableBondCount -0.1114 SsssNcount 0.4174 Optimum Components = 3; n = 32; Degree_of_freedom = 28 r^2 = 0.7681; q^2 = 0.5193; r^2se = 0.2834; q^2se = 0.4081 pred_r^2 = 0.4733; pred_r^2se = 0.3421 F_test = 30.9071; ZScore R^2 = 8.34806; ZScore Q^2 = 4.67148; Best Rand R^2 =0.45204; Best Rand Q^2 =0.13517; Alpha Rand R^2 = 0.00000; Alpha Rand Q^2 = 0.00005; Z Score Pred R^2 = 2.41143; best Rand Pred R^2 = 0.45280; alpha Rand Pred R^2 = 0.01000
Model 2	**06**	2a,2c,2d, 10a,10d,11a, 11b,12b,12c, 12o,12q,12v ,12u	Prediction = 0.9587 SssOE-index = -0.0692 SssNHE-index = -0.0980 Optimum Components = 2; n = 27; Degree_of_freedom = 24 r^2 = 0.7352; q^2 = 0.6037; r^2se = 0.2700; q^2se = 0.3304 pred_r^2 = 0.0268; pred_r^2se = 0.6129 F_test = 33.3191; ZScore R^2 = 9.45919; ZScore Q^2 = 5.38748; Best Rand R^2 =0.28791; Best Rand Q^2 =0.06735; Alpha Rand R^2 = 0.00000; Alpha Rand Q^2 = 0.00000; Z Score Pred R^2 = 0.34605; best Rand Pred R^2 = 0.27968; alpha Rand Pred R^2 = 0.00000
Model 3	**08**	2c,2d,10i,12 b,12g,12i,12 n,12s	Prediction = 0.8009 HydrogensCount = -0.0748 SssCH2count = -0.4304 T_N_N_3 = -0.1767 Optimum Components = 3; n = 32; Degree_of_freedom = 28 r^2 = 0.7264; q^2 = 0.5626; r^2se = 0.2928; q^2se = 0.3703 pred_r^2 = 0.6621; pred_r^2se = 0.3433 F_test = 24.7842; ZScore R^2 = 8.38897; ZScore Q^2 = 7.17676; Best Rand R^2 =0.33372; Best Rand Q^2 =0.11423; Alpha Rand R^2 = 0.00000; Alpha Rand Q^2 = 0.00000; Z Score Pred R^2 = 2.26491; best Rand Pred R^2 = 0.63439; alpha Rand Pred R^2 = 0.05000

MODEL 1: 2D QSAR-RANDOM 80%-SWFB-PLS-TRIAL 3

SssCH2count -0.6682 RotatableBondCount -0.1114 SsssNcount 0.4174
Optimum Components = 3; n = 32; Degree_of_freedom = 28
r^2 = 0.7681; q^2 = 0.5193; r^2se = 0.2834; q^2se = 0.4081
pred_r^2 = 0.4733; pred_r^2se = 0.3421
F_test = 30.9071.

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The model 1 explains 76.81% (r2 = 0.7681) of the total variance in the training set as well as it has internal (q2) and external (pred_r2) predictive ability of 51.93% and 47.33% respectively. The F-test (30.90%) shown the statistical significance of 99.99% of the model is in 10,000. Hence it can be selected as QSAR model. Figure 1 represents the fitness plot between actual and predicted biological activity for training and test sets of model 1.

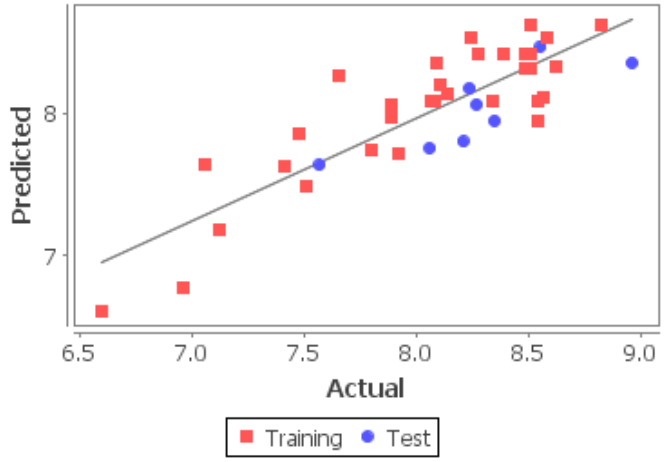

Figure 1: Fitness plot of training and test sets of model 1

The observed and predicted biological activity of training and test sets of molecule was shown in Table 7. The contribution chart of different descriptors of model 1 was depicted in figure 2.

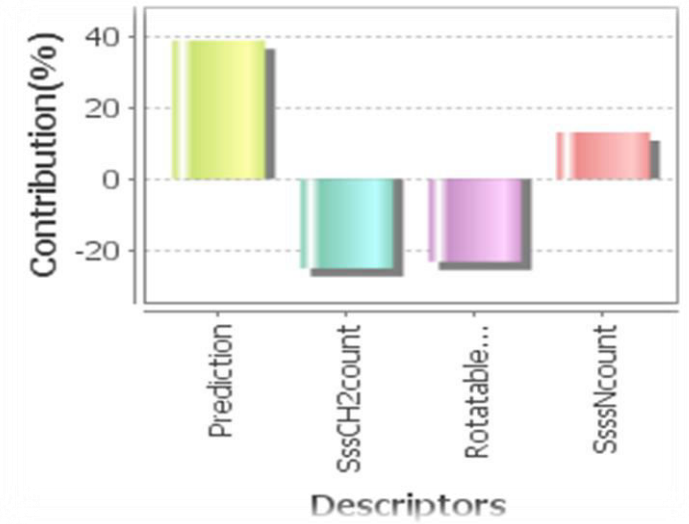

Figure 2: Contribution chart of descriptors for model 1.

Interpretation of result for model 1:

The generated 2D QSAR models reveals that the prediction (0.8014) capability of model 1 was good. The descriptors SssCH2count and Rotablebondcount lies in negative range of -0.6682 and -0.1114 respectively, indicated that negative value is good for DPP IV inhibitory activity. Another descriptor SsssNcount with value of 0.4174 is other important factor governing variation in activity.

Table 7: Actual and predicted activity of Model 1

COMPOUND	ACTUAL	PREDICTED
2a*(Test set)	8.959	8.36152
2b*(Test set)	8.553	8.47295
2c	8.569	8.11319
2d	8.62	8.33947

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10a	8.086	8.36152
10b*(Test set)	8.347	7.95264
10c*(Test set)	8.268	8.06771
10d	8.538	7.95264
10e	8.244	8.54026
10f	8.824	8.62963
10g*(Test set)	8.237	8.18279
10h	7.886	8.07136
10i	6.963	6.78012
10j	7.125	7.18701
10l	7.409	7.63677
11a	7.509	7.49304
11b	6.599	6.61363
11c	8.137	8.14724
11d*(Test set)	8.208	7.80567
12a	7.658	8.2685
12b	8.066	8.08977
12c	7.921	7.71948
12d	7.056	7.64042
12e	7.796	7.74819
12f*(Test set)	7.569	7.64042
12g	8.538	8.09342
12h	8.108	8.20484
12i*(Test set)	8.06	7.75915
12j	7.886	7.982
12k	8.337	8.09342
12m	7.481	7.86378
12n	8.509	8.62848
12o	8.585	8.53911
12p	8.481	8.31627
12q	8.481	8.42769
12r	8.387	8.42769
12s	8.509	8.42769
12t	8.509	8.31627
12u	8.081	8.09342
12v	8.276	8.42769

MODEL 2: 2D QSAR-RANDOM 70%-SWFB-PLS-TRIAL 6
Prediction = 0.9587SssOE-index = -0.0692
SssNHE-index = -0.0980
Optimum Components = 2; n = 27; Degree_of_freedom = 24
r^2= 0.7352; q^2 = 0.6037; r^2se = 0.2700; q^2se = 0.3304
pred_r^2 = 0.0268;pred_r^2se = 0.6129
F_test = 33.3191
The model 2 explains 73.52% (r2 = 0.7352) of the total variance in the training set as well as it has internal (q2) and external (pred_r2) predictive ability of 60.37% and 02.68% respectively. The F-test (33.31%) shown the statistical significance of 99.99% of the model is in 10,000. Hence it can be selected as QSAR model. Figure 3 represents the fitness plot between actual and predicted biological activity for training and test sets of model 2.

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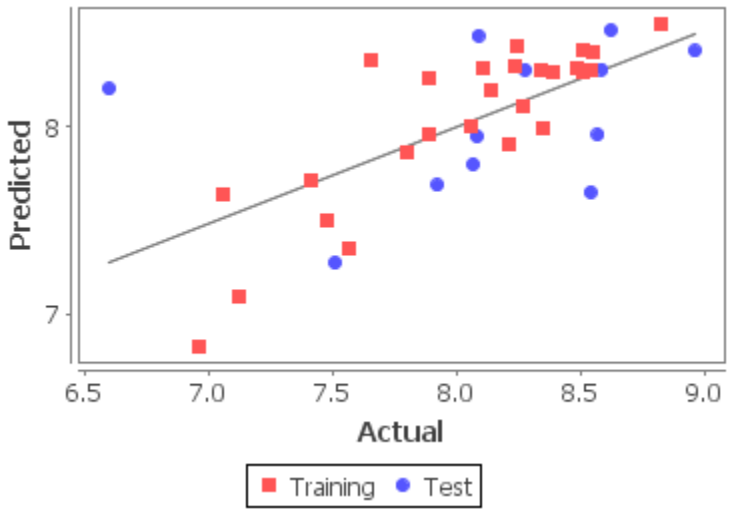

Figure3: Fitness plot of training and test sets of model 2

The observed and predicted biological activity of training and test set of molecules was shown in Table 8. The contribution chart of different descriptors of model 2 was depicted in figure 4.

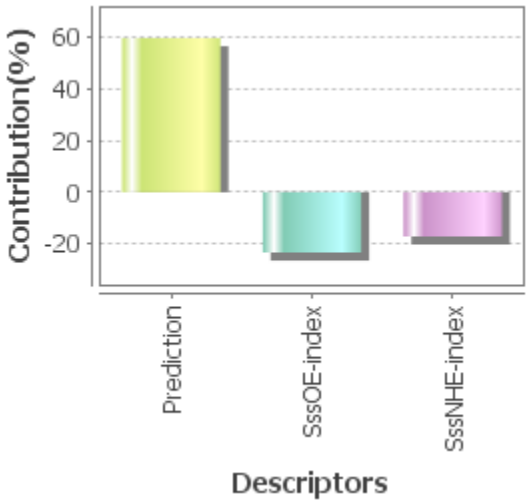

Figure 4: Contribution chart of descriptors for model 2.

Interpretation of result for model 2:

The generated 2D QSAR models reveals that the prediction (0.9587) capability of model 2 was good. It can be seen that in the present study, PLS (coupled with stepwise forward- backward variable selection) led to a statistical significant model. The developed PLS model reveals that the descriptors SssOE-index and SssNHE-indexplays an important role in determining DPP IV inhibitory activity. The descriptors SssOE-index and SssNHE-index lies in negative range of -0.0692and-0.0980respectively, indicated that negative value was good for DPP IV inhibitory activity.

Table 8: Actual and predicted activity of Model 2

COMPOUND	ACTUAL	PREDICTED
2a*(Test set)	8.959	8.40561
2b	8.553	8.39701
2c*(Test set)	8.569	7.96026
2d*(Test set)	8.62	8.5167
10a*(Test set)	8.086	8.48769
10b	8.347	7.99446
10c	8.268	8.11709
10d*(Test set)	8.538	7.65255

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10e	8.244	8.43395
10f	8.824	8.5546
10g	8.237	8.32504
10h	7.886	8.26007
10i	6.963	6.83443
10j	7.125	7.10159
10l	7.409	7.71724
11a*(Test set)	7.509	7.27659
11b*(Test set)	6.599	8.20412
11c	8.137	8.19524
11d	8.208	7.91174
12a	7.658	8.35714
12b*(Test set)	8.066	7.80008
12c*(Test set)	7.921	7.69001
12d	7.056	7.64012
12e	7.796	7.87071
12f	7.569	7.35184
12g	8.538	8.30569
12h	8.108	8.30966
12i	8.06	8.00378
12j	7.886	7.96601
12k	8.337	8.30841
12m	7.481	7.50015
12n	8.509	8.41499
12o*(Test set)	8.585	8.30807
12p	8.481	8.3193
12q*(Test set)	8.481	8.31941
12r	8.387	8.29453
12s	8.509	8.29453
12t	8.509	8.30569
12u*(Test set)	8.081	7.95025
12v*(Test set)	8.276	8.30494

MODEL 3: 2D QSAR-RANDOM 80%-SWFB-PLS-TRIAL 8
Prediction = 0.8009HydrogensCount = -0.0748
SssCH2count = -0.4304T_N_N_3 = -0.1767
Optimum Components = 3; n = 32; Degree_of_freedom = 28
r^2= 0.7264; q^2 = 0.5626; r^2se = 0.2928; q^2se = 0.3703
pred_r^2 = 0.6621;pred_r^2se = 0.3433
F_test = 24.7842
The model 3 explains 72.64% (r2 = 0.7264) of the total variance in the training set as well as it has internal (q2) and external (pred_r2) predictive ability of 56.26% and 66.21% respectively. The F-test (24.78%) shown the statistical significance of 99.99% of the model is in 10,000. Hence it can be selected as QSAR model. Figure 5 represents the fitness plot between actual and predicted biological activity for training and test sets of model 3.

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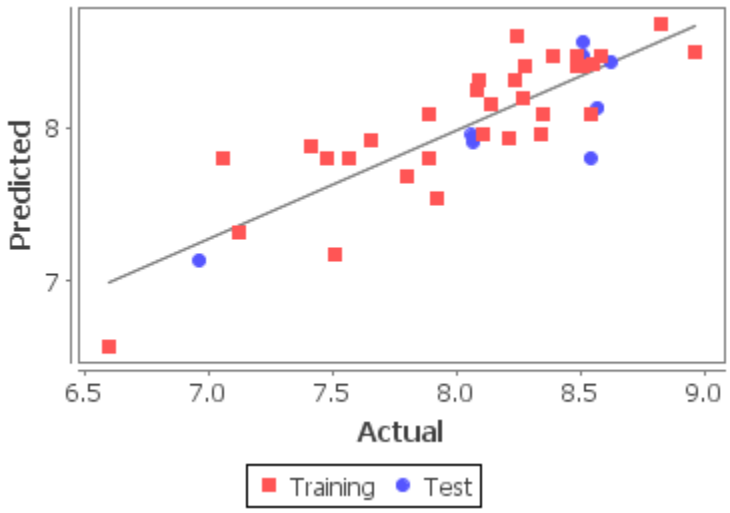

Figure 5: Fitness plot of training and test sets of model 3

The observed and predicted biological activity of training and test set of molecules was shown in Table 9. The contribution chart of different descriptors of model 3 was depicted in figure 6.

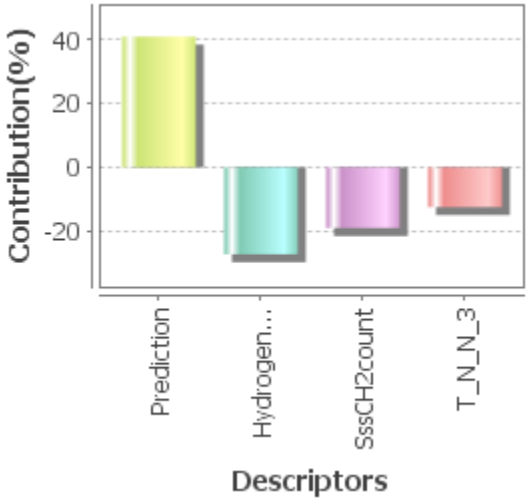

Figure 6: Contribution chart of descriptors for model 3.

Interpretation of result for model 3:

The generated 2D QSAR models reveals that the prediction (0.8009) capability of model 3 was good. It can be seen that in the present study PLS (coupled with stepwise forward- backward variable selection) led to a statistical significant model. The developed PLS model reveals that the descriptors SssCH2count, HydrogensCountand T_N_N_3plays an important role in determining DPP IV inhibitory activity. All the three descriptors lies in negative range of -0.4304, -0.0748 and -0.1767 respectively, indicated that negative value was good for DPP IV inhibitory activity.

Table 9: Actual and predicted activity of Model 3

COMPOUND	ACTUAL	PREDICTED
2a	8.959	8.49576
2b	8.553	8.421
2c* (Test set)	8.569	8.13622
2d*(Test set)	8.62	8.43555
10a	8.086	8.31901
10b	8.347	8.08713
10c	8.268	8.20213
10d	8.538	8.08713

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10e	8.244	8.59962
10f	8.824	8.68893
10g	8.237	8.31713
10h	7.886	8.09285
10i*(Test set)	6.963	7.13806
10j	7.125	7.32198
10l	7.409	7.88281
11a	7.509	7.17246
11b	6.599	6.5791
11c	8.137	8.16189
11d	8.208	7.93188
12a	7.658	7.91764
12b*(Test set)	8.066	7.91576
12c	7.921	7.54571
12d	7.056	7.80075
12e	7.796	7.68575
12f	7.569	7.80075
12g*(Test set)	8.538	7.80648
12h	8.108	7.956
12i*(Test set)	8.06	7.956
12j	7.886	7.80648
12k	8.337	7.956
12m	7.481	7.80442
12n*(Test set)	8.509	8.56863
12o	8.585	8.47932
12p	8.481	8.40456
12q	8.481	8.47932
12r	8.387	8.47932
12s*(Test set)	8.509	8.47932
12t	8.509	8.40456
12u	8.081	8.25504
12v	8.276	8.40456

SUMMARY AND CONCLUSION:

In present 2D QSAR work, an attempt has been made to identify the necessary requirements in terms of substituents and structure. Two dimensional Qsar models has been developed by means of random selection method with different percentage associated with stepwise forward and backward method and by means of partial square regression analysis. Three best 2D QSAR models were developed with good internal as well as external values. Various descriptors with different values provide an insight that the developed model has capability of good inhibitory activity against DPP IV enzyme. At last, it was concluded that the present work provide an understanding between various physicochemical parameters with different structures and their biotic activity by which future researchers can develop more potent substituted pyrrolidine derivatives.

CONFLICT OF INTEREST: The authors declared no conflict of interest.

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