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3D QSAR Analysis of some (2-benzylcarbamoyl-phenoxy)-acetic acid derivatives for treatment of chronic diabetic complications

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ABSTRACT

3D quantitative structure activity relationship study was performed on a series of some (2-benzylcarbamoyl-phenoxy)-acetic acid derivatives for treatment of chronic diabetic complications for establishing n quantitative relationship between biological activity and their physicochemical properties. Several statistical regression expressions were obtained with 3D-QSAR study using k-Nearest Neighbor (kNN) method and four statistical significant models were generated by using Sphere Exclusion method and Randon Selection Method. By kNN Sphere Exclusion Method (q2= 0.5042 , 0.6433 and pred_r^2= 0.6939, 0.7115 for model 1 and 2 respectively) and kNN Randon Selection Method (q2= 0.6297, 0.7107 and pred_r^2=0.8970,0.5908 for model 3,4 respectively).

Key words: 3DQSAR, chronic diabetic, statistical regression, kNN method

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INTRODUCTION

Diabetes mellitus and its disabling complications, which include blindness, renal failure, neuropathy, limb amputation, myocardial infarction, and stroke affect some 17 million people in the United States with an estimated cost of over 100 billion dollars annually.[1]

Through various clinical studies, including the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), the development and progression of these complications in type I and type II patients has been clearly linked to elevated blood glucose levels.2,3 During euglycemic conditions glucose is preferentially metabolized through the glycolytic pathway where it is phosphorylated with ATP by hexokinase to form glucose-6-phosphate. However, during conditions of hyperglycemia, as observed in diabetes mellitus, elevated blood glucose levels saturate the normal pathways of glucose metabolism and a dramatic increase in flux through the polyol pathway results.

Quantitative Structure activity relationship (QSAR) are computational statistical methods which reveals explainable difference in the observable biological activity. It is imperative to improve predictability of QSAR model of test compounds by considering the structural and physicochemical features. 3-Diamensional Quantitative Structure activity relationship techniques including k-Nearest Neighbor (kNN) method could facilitate in designing unsynthesized agents for therapeutic purpose. This technique predict the activities based on the existing set of molecules, kNN develops the 3D-Quantitative Structure activity relationship between the steric, electrostatic and hydrophobic properties. This data helps to understand the structural basis for their affinity for the activity and to design still better potent molecules.

MATERIALS AND METHODS

1. DATA SELECTION-

In the present study a dataset of 48 molecules of some (2-benzylcarbamoyl-phenoxy)-acetic acid derivatives were used which were reported to have for treatment of chronic diabetic complications. chronic diabetic complications data listed in Table No. 01 (n=48), have been used in this study. The some (2-benzylcarbamoyl-phenoxy)-acetic acid derivatives were drawn in the 2D Draw application in Tool menu of QSAR Plus of Molecular Design Suit [MDS] software[10]. Ref.and then exported to QSAR Plus window (2D structure converted to 3D structure by using VLife MDS software. The activity data is given in IC50 (nM) value.All compounds have been converted to the logarithmic scale [pIC50 (moles)], and then used for subsequent QSAR analysis as the response variables. pIC50 data saved as .txt. file. After the conversion, structures are saved as .mol2 file in QSAR Plus 3D window.

2. ENERGY MINIMIZATION-

Energy minimization is done by using the force field or minimizing energy with the help of MMFF force field which result in the optimization of the geometry of the molecule. After drawing all the molecules they were again optimized by using batch minimize option using MMFF force field and optimized molecules were used to calculate the physicochemical and alignment descriptors.

3. DESCRIPTORS EVALUATION-

In these steric, electrostatic and hydrophobic pararameters calculated.

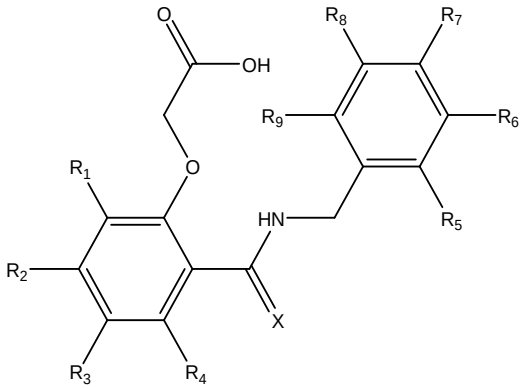
4. DATA SELECTION-

For model development in 3D-QSAR analysis three methods Random selection method, Manual data selection method, Sphere Exclusion method were used for creation of training and test set and 10 trials were run in each case[38]. In this paper we have selected Sphere Exclusion Method and Random Selection method by differing dissimilar values. After the creation of training and test set, minimum and maximum value of the test and training set is checked, using the QSAR tool, then the statistical method like kNN method used for model building.

5. VARIABLE SELECTION-

kNN method Stepwise variable selection (forward, forward-backwar andbackward), Simulated annealing, and Genetic algorithm method is used. For creation of training and test set same method were applied as 3D-QSAR analysis.

Table 1. Physical and in vitro inhibitory properties of (2-benzylcarbamoyl-phenoxy)-acetic acid ARIs



Compound	Substitution	X	IC50	pIC50
1	2-F, 3-CH3, 5-F, 7-Br	S	24	7.619788758288394
2	2-F, 3-CH3, 5-F, 7-Br	O	24	7.619788758288394
3	2-Cl	O	3300	5.481486060122113
4	2-Cl, 7-OCH	O	8800	5.055517327849831
5	2-Cl, 7-CF3	O	10000	5
6	2-Cl, 7-Br	O	550	6.259637310505757
7	2-Cl, 5-F, 7-Br	O	30	7.522878745280337
8	2-F, 5-F, 7-Br	O	55	7.259637310505756
9	2-F, 5-F, 7-Br	S	30	7.522878745280337
10	2-Cl, 7-Cl	O	1300	5.886056647693163
11	2-Cl, 6-Cl, 7-Cl	O	34	7.468521082957745
12	2-Cl, 6-NO2	O	6	8.221848749616356
13	2-F, 6-NO2, 7-CH3	O	8	8.096910013008056
14	2-Cl, 6-F	O	820	6.086186147616283
15	2-Cl, 6-CF3	O	39	7.4089353929735005
16	2-Cl, 6-CF3, 8-F	O	29	7.537602002101044
17	2-Cl, 6-CF3, 8-CF3	O	22000	4.657577319177794
18	2-Cl, 6-OCH3, 8-OCH3	O	4800	5.318758762624412
19	2-Cl, 5-F, 9-F	O	730	6.136677139879545
20	5-F, 7-Br	O	176	6.7544873321858505
21	2-CH3, 5-F, 7-Br	O	630	6.200659450546418
22	2-CF3, 5-F, 7-Br	O	2400	5.619788758288394
23	2-OCH3, 5-F, 7-Br	O	550	6.259637310505757
24	2-SCH3, 5-F, 7-Br	O	83	7.080921907623926
25	2-SO2CH3, 5-F, 7-Br	O	13000	4.886056647693164
26	2-F, 3-F, 5-F, 7-Br	O	37	7.431798275933005
27	2-F, 3-F, 5-F, 7-Br	S	33	7.481486060122113
28	2-F, 4-F, 5-F, 7-Br	O	820	6.086186147616283
29	3-F, 5-F, 7-Br	O	150	6.823908740944319
30	3-Br, 5-F, 7-Br	S	64	7.193820026016113
31	3-Br, 5-F, 7-Br	O	37	7.431798275933005
32	3-CH3, 5-F, 7-Br	O	69	7.161150909262744
33	3-NH2, 5-F, 7-Br	O	8300	5.080921907623926
34	3-NO2, 5-F, 7-Br	O	200	6.698970004336019
35	3-OH, 5-F, 7-Br	O	470	6.327902142064283
36	3-OCH3, 5-F, 7-Br	O	100	7
37	2-F, 6-NO2	O	8	8.096910013008056
38	3-OCH2CH2CH3, 5-F, 7-Br	O	3100	5.508638306165728
39	2-F, 3-Br, 6-NO2	O	6	8.221848749616356
40	2-F, 3-CN, 6-NO2	O	7	8.154901959985743
41	2-F, 3-Ph, 6-NO2	O	8	8.096910013008056
42	2-F, 3-Ph, 6-NO2	S	11	7.958607314841775
43	2-F, 3-CH3, 6-NO2	O	8	8.096910013008056
44	2-F, 3-CH3, 6-NO2	S	7	8.154901959985743
45	3-CH3, 6-NO2	O	11	7.958607314841775
46	3-OCF3, 6-NO2	O	9	8.045757490560675
47	3-OCF3, 6-NO2	S	12	7.920818753952375
48	2-F, 6-NO2	S	6	8.221848749616356

RESULTS AND DISCUSSION

All the 48 molecules of the selected series were subjected to various regression analysis, the following significant 3D-QSAR models with equations were obtained for treatment of chronic diabetic complications**.** (Table-02)

Table-02: List of predictive QSAR models with equation generated from various regression methods

<table>
<tr><td>METHOD</td><td>MODEL 01</td><td>MODEL 02</td></tr>
<tr><td>Sphere Exclusion Method</td><td>Dissimilarity value-8</td><td>Dissimilarity value-6.5</td></tr>
<tr><td></td><td>kNN Method
Training Set Size = 40
Test Set Size = 8
Selected Descriptors:
E_579
E_261
Statistics:
<table><tr><td>k Nearest Neighbour</td><td>2</td></tr><tr><td>N</td><td>40</td></tr><tr><td>Degree_of_freedom</td><td>37</td></tr><tr><td>q2</td><td>0.5042</td></tr><tr><td>q2_se</td><td>0.7296</td></tr><tr><td>pred_r2</td><td>0.6939</td></tr><tr><td>pred_r2se</td><td>0.7602</td></tr></table>
Descriptor Range:
E_579 -4.5947 -3.5668
E_261 -0.6792 -0.2934</td><td>kNN Method
Training Set Size = 33
Test Set Size = 15
Selected Descriptors:
E_600
E_732
Statistics:
<table><tr><td>k Nearest Neighbour</td><td>3</td></tr><tr><td>n</td><td>33</td></tr><tr><td>Degree_of_freedom</td><td>30</td></tr><tr><td>q2</td><td>0.6433</td></tr><tr><td>q2_se</td><td>0.6509</td></tr><tr><td>pred_r2</td><td>0.7115</td></tr><tr><td>pred_r2se</td><td>0.6024</td></tr></table>
Descriptor Range:
E_600 -3.9772 -1.3055
E_732 -0.0125 -0.0088</td></tr>
</table>

<table>
<tr><td>METHOD</td><td>MODEL 03</td><td>MODEL 04</td></tr>
<tr><td>Manual Selection Method</td><td>Percentage for selecting data 70%</td><td>Percentage for selecting data 80%</td></tr>
<tr><td></td><td>kNN Method
Training Set Size = 33
Test Set Size = 15
Selected Descriptors:
E_732
E_600
E_578
Statistics:
<table><tr><td>k Nearest Neighbour</td><td>4</td></tr><tr><td>n</td><td>33</td></tr><tr><td>Degree_of_freedom</td><td>29</td></tr><tr><td>q2</td><td>0.6297</td></tr><tr><td>q2_se</td><td>0.6723</td></tr><tr><td>pred_r2</td><td>0.8970</td></tr><tr><td>pred_r2se</td><td>0.3540</td></tr></table>
Descriptor Range:
E_732 -0.0096 -0.0059
E_600 0.0602 0.3440
E_578 -0.0030 -0.0024</td><td>kNN Method
Training Set Size = 38
Test Set Size = 10
Selected Descriptors:
H_814
E_622
H_265
E_38
S_200
E_263
S_670
Statistics:
<table><tr><td>k Nearest Neighbour</td><td>3</td></tr><tr><td>n</td><td>38</td></tr><tr><td>Degree_of_freedom</td><td>30</td></tr><tr><td>q2</td><td>0.7107</td></tr><tr><td>q2_se</td><td>0.5536</td></tr><tr><td>pred_r2</td><td>0.5908</td></tr><tr><td>pred_r2se</td><td>0.8440</td></tr></table>
Descriptor Range:
H_814 -0.0393 0.3907
E_622 -0.1041 0.6508
H_265 0.2108 0.4900
E_38 -0.5677 0.3250
S_200 4.6183 6.5590
E_263 10.0000 10.0000
S_670 -0.0186 -0.0160</td></tr>
</table>

The QSAR models presented in table no. 02, in which n is the number of data points used in the model. Pred_ r2 is the predicted r2 for external test set and se is the standard error of estimate (smaller is better). From the table no. 02, the equation of Model-01 explains internal (q2) and external (pred_r2) predicative ability . internal (q2=0.5042, 0.6433, 0.6297,and 0.7107 for model 01, 02, 03 and 04 respectivel)., external (pred_r2) predicative ability (pred_r2= 0.6939, 0.7115, 0.8970 and 0.5908 for model 01, 02, 03 and 04 respectivel).

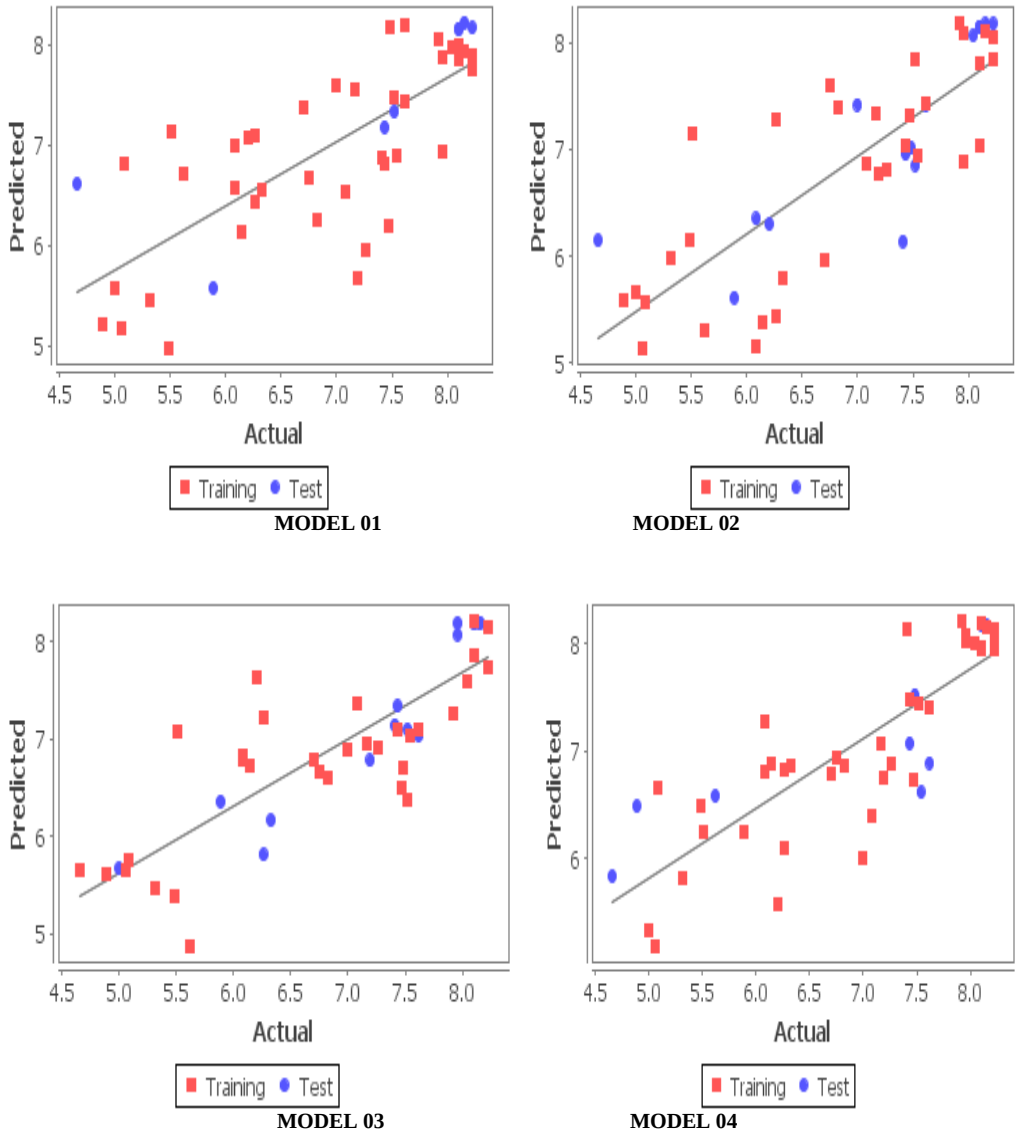


Fig.02- Fitness graphs were plotted between the actual and the predicted biological activities for model 01,02 ,03and 04 respectively.

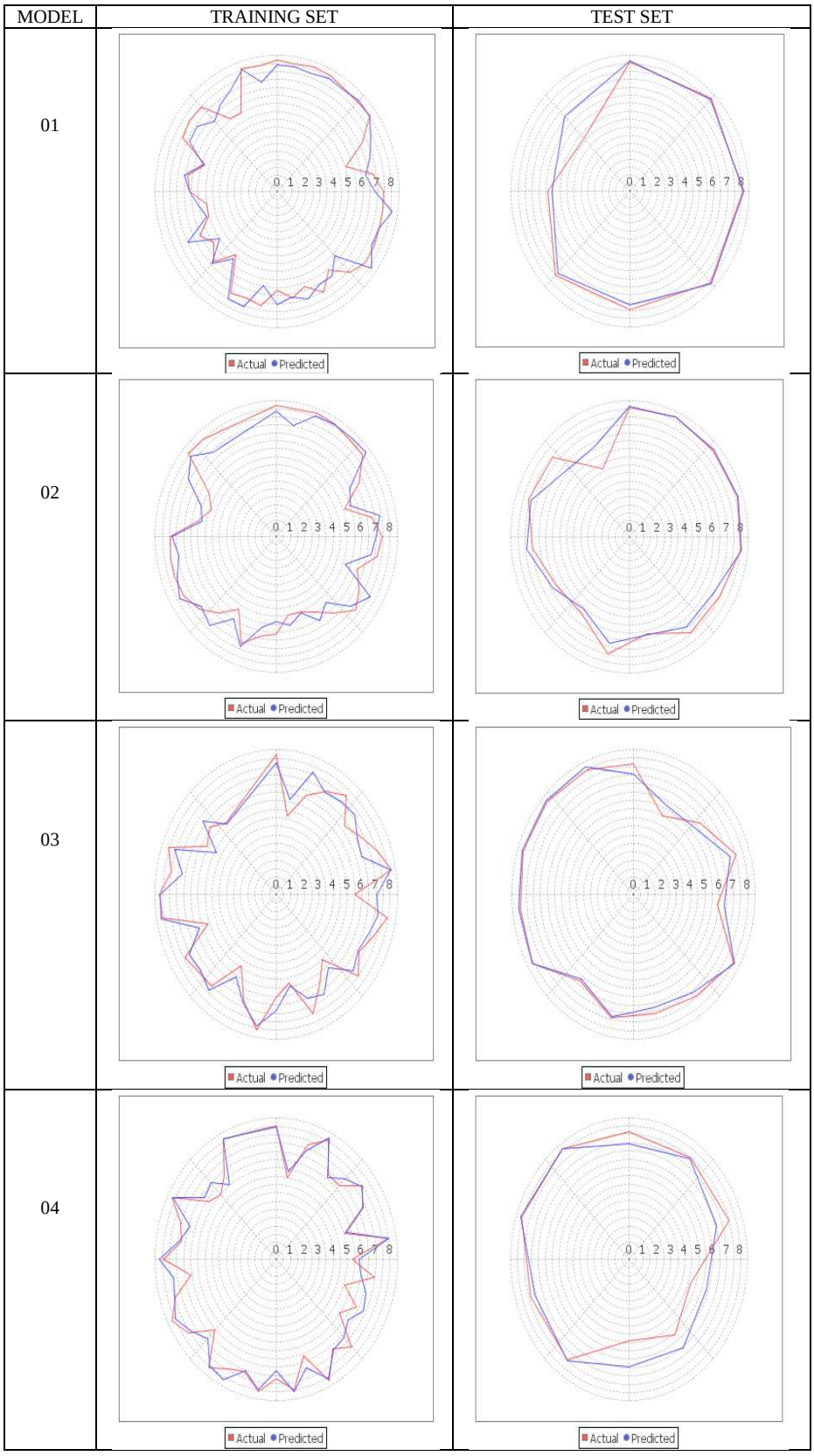
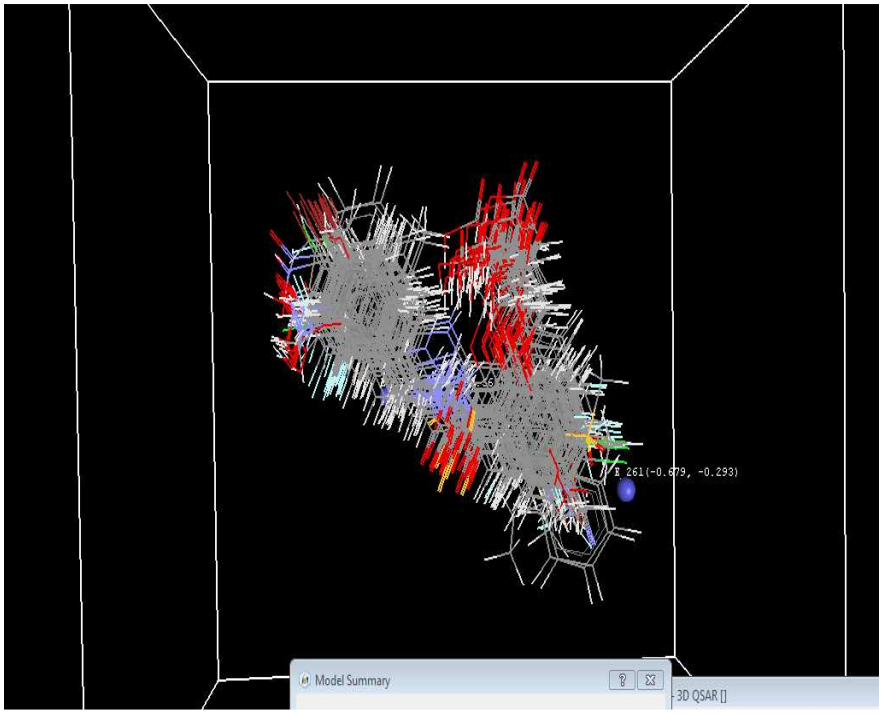
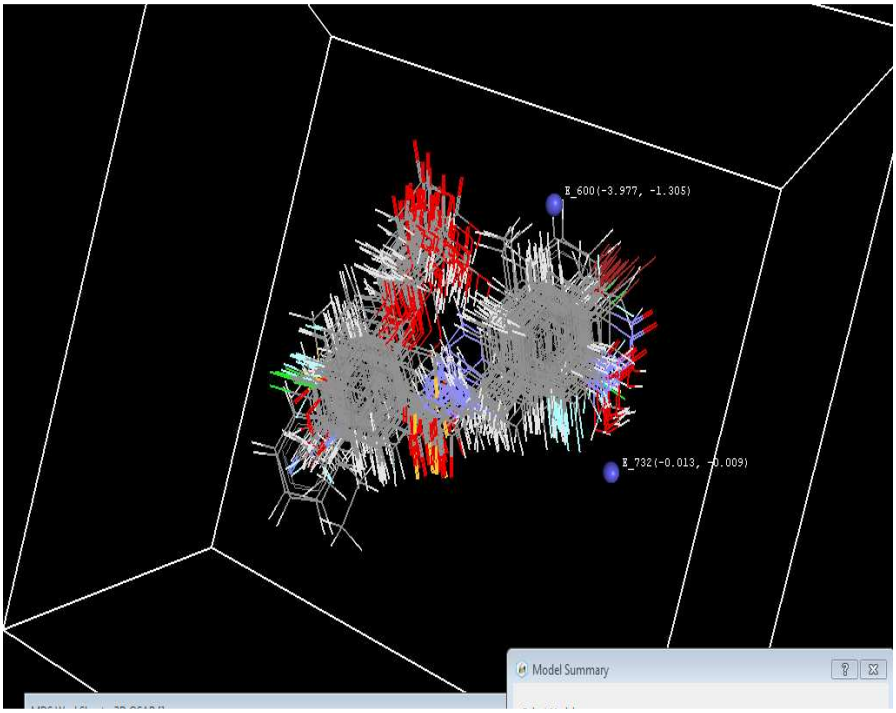


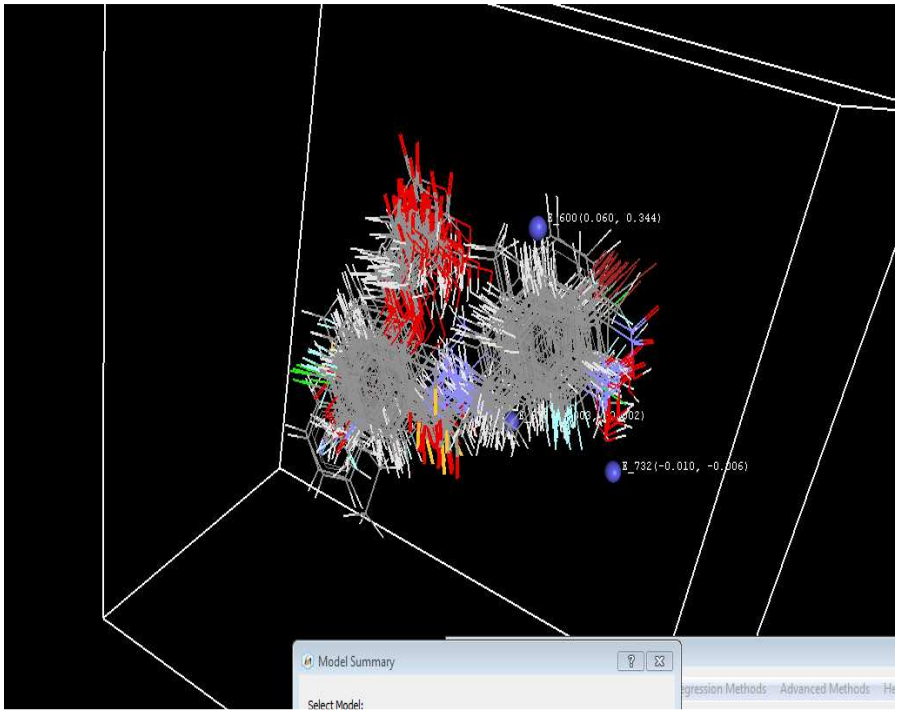
Figure-3: Graph between actual and predicted biological activity for training and test set of Model-01, 02, 03 and 04 model



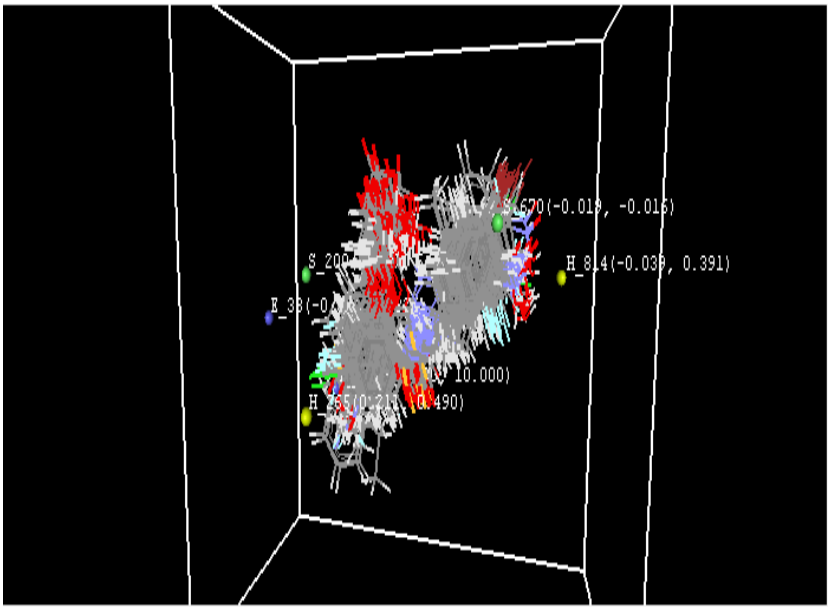
MODEL 01



MODEL 02



MODEL 03



MODEL 04

Figure-4: kNN-MFA result plot- 3D-alignment of molecules with the electrosatstic point in parenthesis for model 01, 02, 03 and 04

This model indicates that one electrostastic, and steric descriptor is involved. kNN-MFA result plot in which 3D-alignment of molecules with the important electrostastic, point contributing with model with ranges of values shown in parenthesis represented in Figure-4.

CONCLUSION

In the present study an attempt has been made to identify the necessary structural requirements molecule for activity. From the present 3D QSAR analysis, four best models were generated two Model from kNN (Sphere Exclusion Method) and two Model from (Random SelectionMethod)among which can be used for predicting the activity of the newly designed compounds in finding some more potent molecule. Finally, it is concluded that model 03 is the best model as it having q2 value=0.6297 and pred_r2 value =0.8970. The work presented here will play an

important role in understanding the relationship of physiochemical parameters with structure and biological activity. By studying the QSAR model one can select the suitable substituent for active compounds with maximum potency.

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