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Pharmacophore Mapping, Docking and Three Dimensional QSAR Analysis of [(S)- γ -(Arylamino) Prolyl] Thiazolidine Compounds As A Potent and Stable DPP-IV Inhibitors

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ABSTRACT

Novel DPP-IV (Dipeptidyl peptidase-IV) inhibitors were designed based on a previously described series diabetes. Despite years of continual efforts, diabetes is still one of the most dangerous diseases in the world. The enzyme which increases the level of glucose in the body is DPP-IV. Inhibition of DPP-IV is currently explored as a novel therapy for treatment of type 2 diabetes. In view of that we have attempt to design a novel DP-IV inhibiting agents through molecular modeling. Essential pharmacophoric feature were identified using ligand Scout. The common pharmacophoric features were identified by Pharmacophore mapping, three pharmacophoric sites were found to be hydrogen bond acceptor and other two were hydrogen bond donor. Pharmacophoric feature is shown by color coding. In addition docking study was also performed using Molegro 5.0, to establish theoretical drug receptor interaction between ligands and DPP-IV enzyme. It was found that all the ligands formed a hydrogen bond interaction with His 740 of DPP-IV enzyme. The unbound His 740 is essential for the inhibition of DPP-IV enzyme The multi parameter 3D QSAR models have also generated, described relationship of DPP-IV inhibitory activity and physiochemical parameters, result can be used for structure optimization. Among several 3D QSAR model, two models with good statistical values were selected. Activity of model 1 and model 2 with good correlation coefficient was (0.6357 and 0.8470) and internal predictivity was (0.9744 and 0.6741). The results are promising and can be used to design novel DPP-IV inhibiting agents.

KEYWORDS: 3D-QSAR, pharmacophoric mapping, DPP IV inhibitors, [(s)-γ-(arylamino)prolyl] thiazolidine derivatives, Docking, molecular modeling

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INTRODUCTION

Diabetes mellitus is a metabolic disorder it is major public health issue all over the world. Recent WHO calculations indicate that worldwide almost 3 million deaths per year are attributable to diabetes.[1] Main cause of type 2 diabetes is glucagon-like peptide-1 and DPP-4 enzyme. Treatment can be provoked by inactivation of glucagon-like peptide-1 (GLP-1) by inhibition of the enzyme dipeptidyl peptidase-4 (DPP-4).[2-4] Over the past decades, researcher has focused on the design of reversible and irreversible inhibitors of DPP IV activity and bitterly considering on the therapeutic potential of these compounds[5]. DPP-4 inhibition has thereby been demonstrated to be anti diabetic both in animal models of diabetes [6–9] and in patients with type 2 diabetes.[10-12] Our study is intentionally focused on pharmacophore modeling, docking and QSAR.

The pharmacophore modeling approach was helpful in providing guidance for the rational design to discover novel DPP-4 inhibitors by highlighting the important binding features of DPP-4 inhibitors ligands. A pharmacophore model can be interpreted as a spatial arrangement of atoms or functional groups that are considered to be responsible for biological activity.[13]

Rational Drug Design helps to facilitate and fasten and improves the drug designing process, which involves various methods to identify novel compound, out of them one method is the docking of molecule of drug with the receptor. The therapeutic action of the drug will be under consideration when the biochemical pathway of the enzyme can be exploited.[14]

Docking study has been used in modern drug designing to understand drug–receptor interaction. It has been shown in the literature that computational procedures may strongly support and help the design of new, more potent drugs by revealing the mechanism of drug-receptor interaction.[15]

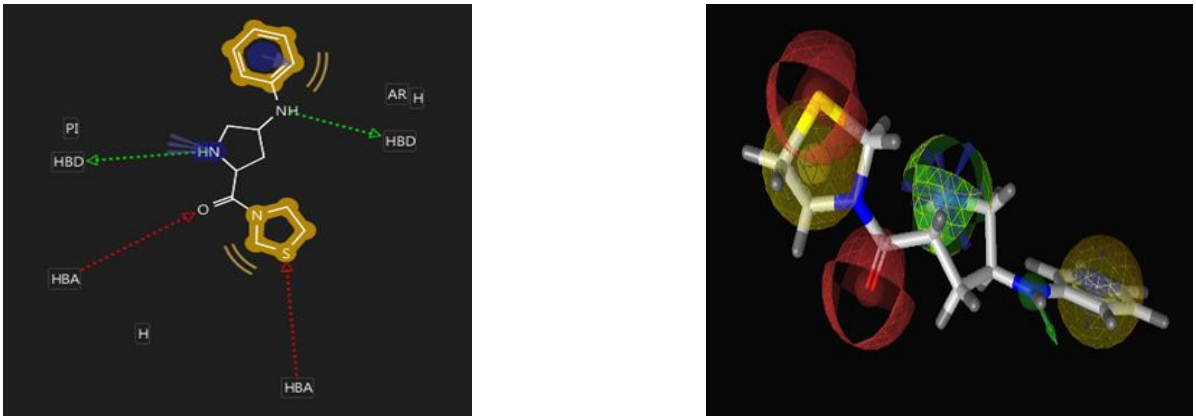
Focused QSAR study is to establish quantitative relationship between physiochemical properties and biological activities of the compounds in order to search for novel thiazolidine derivatives that would show a promise to become useful DPP-IV inhibitors. A series is taken from literature[16] which were reported as DPP-IV inhibitory activity selected for QSAR study using Vlifemds software[17].

MATERIALS AND METHODS

In the present study a data set of [(s)-γ-(arylamino)prolyl] thiazolidine derivatives (13 molecules) has been taken from the literature[16]. CS Chem Office 8.0 was used for the sketching of molecules. The sketched 2D structures were transformed into 3D structures using module of the program (Chem3D Ultra 8.0) and further minimization of energy performed with reported structure.

Pharmacophore mapping

The energy minimized structure of all thiazolidine derivatives saved as .pdb format using Chem3D Ultra 8.0 for pharmaciophore mapping. The .pdb files were submitted one by one to strutured-based pharmacophore generation module of Ligand Scout for re-optimazation for energy. The data from strutured-based transfered to ligand based and finally to alignment view. This process was repeated for the whole set of compounds included in the training set along with one standard drug. After generation of the pharmacophore, the alignment tab was clicked. The process proceeded with the selection of pharmacophores, and then, the ‘‘Create shared pharmacophore’’ button was clicked. This was set as reference, and all the ligands were selected and correspondingly aligned to this pharmacophore. Thus, a shared pharmacophore was generated. Pose of pharmacophoric ligand 1 is shown in figure 1.

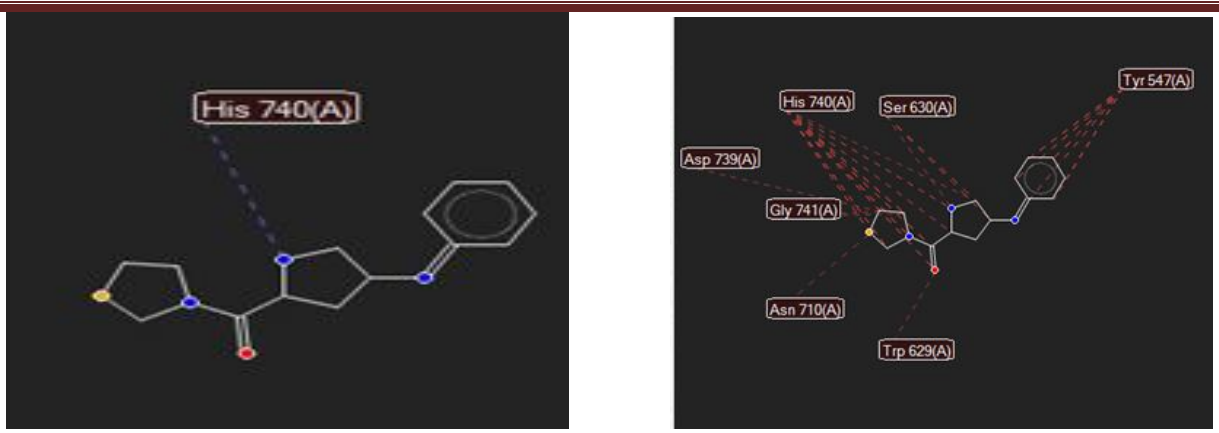


A B

Fig 1: Ligand 1 nature of the atom is shown in A, B picture and color line shows the bonding.

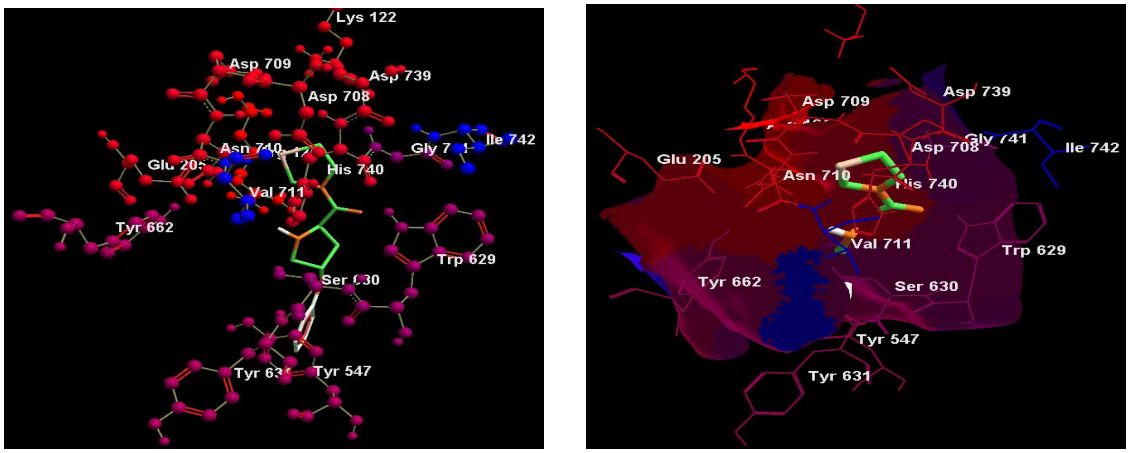
Docking studies

Protein ligand docking studies were carried out based on the basis of crystal structure of protein Pdb 3OLE and ligand binding. All solvents molecule, cofactor and co-crystallized ligands were removed from structures. Molecular docking calculations for all compounds were under taken using molegro virtual docker 5.0. The reference compound taken in docking is Vildagliptin. The parameter selected in the docking studies were moldock optimizer, number of runs 10, population size 50, cross over rate 0.90 and max iteration 2000 and cavity selected is user define. The hydrogen bond interaction and hydrophobic bond interaction is shown in the figure 2 and figure 3. The interaction of ligand with receptor and cavity has shown in figure 4. The selected cavity volume is 7209.98 and surface is 775.68. The docking score were generated by automated process of Molegro shown in Table 1.



A B

Fig2. The Diagram A shows hydrogen bond interaction with His 740 and hydrophobic interaction of ligand 1 with the receptor.



A *B*

Fig 3. The Diagram A shows hydrogen bond interaction and B shows hydrophobic interaction ligand 1 with the protein 3OLE.

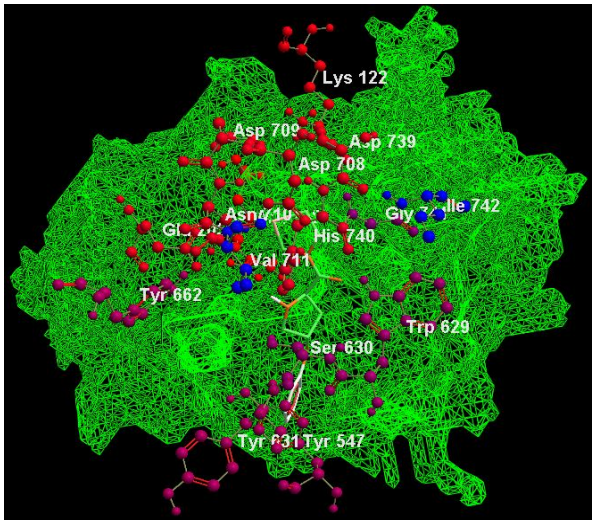


Fig 4. The picture shows the interaction of ligand 1 with receptor and cavity.

Table 1 The docking score of compound

S. No.	Ligand	MolDock Score	Rerank Score	H Bond
1.	12a	-71.2508	-57.8901	-2.5
2.	12b	**-83.6954**	-51.8349	-3.79632
3.	12c	**-85.3678**	-50.2989	-4.99963
4.	12d	-78.4394	-58.5535	-2.5
5.	12e	**-86.0359**	-15.8717	-0.197609
6.	12f	-78.1525	-63.7493	-3.71606
7.	12g	-78.2444	-63.8925	-3.65214
8.	12h	-75.5394	-61.6064	-1.51947
9.	12i	-80.632	-59.5268	-2.5
10.	12j	-79.9659	-50.9232	-6.47779
11.	12k	**-82.8949**	-47.2691	-2.5
12.	12l	-78.4415	14.444	-1.66372
13.	12m	**-84.3965**	-57.9185	-2.5
14.	Vildagliptin	**-82.228**	-59.1289	-2.5

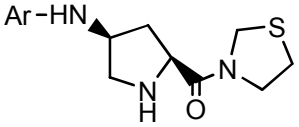
3D QSAR studies

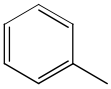
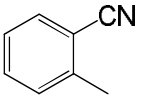
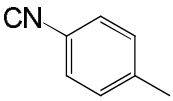
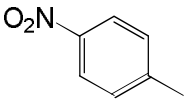
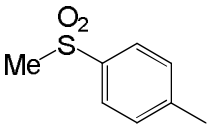
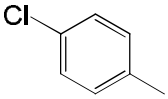
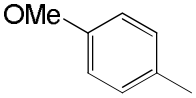
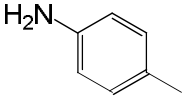
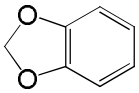
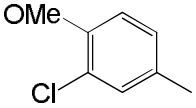
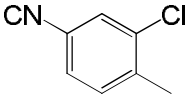
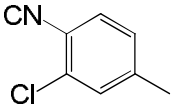
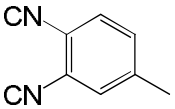
Data Set: In the present study a data set of [(s)-γ-(arylamino)prolyl] thiazolidine derivatives (13 molecules) has been taken from the literature[16] for QSAR studies reported in table 2. The reported IC50 values (nM), had been changed to the logarithmic scale [pIC50 (moles)], for QSAR study.

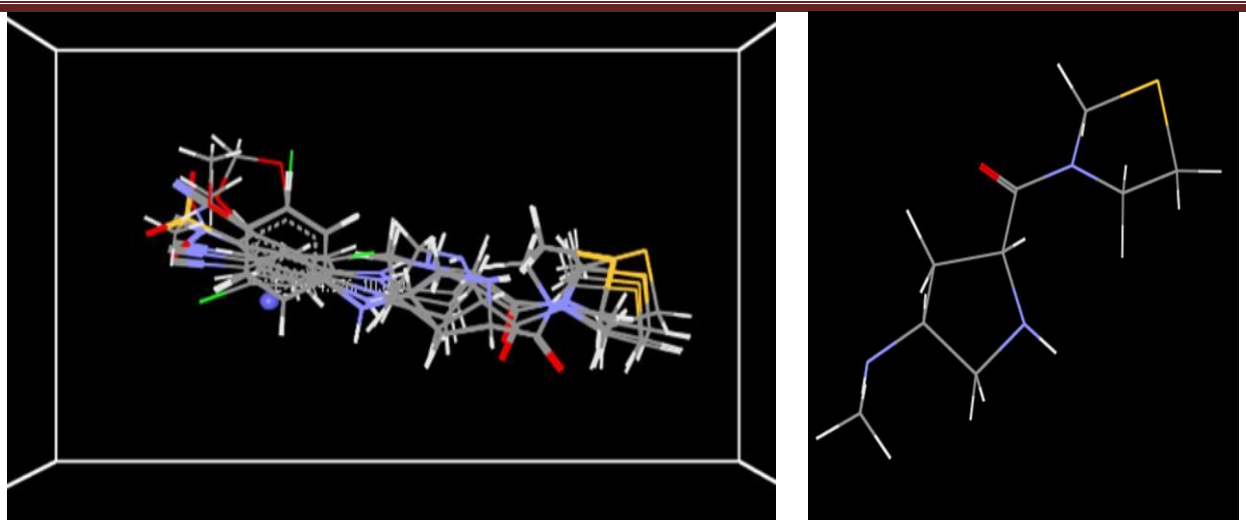
Modeling study was performed on XP operating system using the software Molecular Design Suite (MDS) 4.1.19092011. The selected dataset were aligned by using template based alignment method. The alignment of all the molecules on (1) and template on (2) is shown in figure 5.

Descriptor calculation: Once the molecules are aligned, a molecular field is computed on a grid of points in space around the molecule. This field provides a description of how each molecule will tend to bind in the active site. Descriptors representing the steric, electrostatic and hydrophobic interaction energies were computed.

Table 2 General structure of the compounds of [(s)-γ-(arylamino)prolyl] thiazolidine derivatives and their biological activities (data set of 13 molecules)



S.no	Compound	Ar	IC50 (nM)	log(1/IC50)
1.	12a		147	6.833
2.	12b		24.1	7.618
3.	12c		25.2	7.598
4.	12d		19.2	7.717
5.	12e		52.3	7.281
6.	12f		45.4	7.345
7.	12g		51.5	7.29
8.	12h		105	6.979
9.	12i		29.0	7.538
10.	12j		19.9	7.701
11.	12k		18.2	7.74
12.	12l		11.1	7.955
13.	12m		8.4	8.076



1 2

Figure 5: Aligned Molecule structure (1) and Template structure (2)

Data selection: In order to evaluate the QSAR model externally, data set was divided into training and test set using sphere exclusion methods. Training set is used to develop the QSAR model for which biological activity data are known. Test set is used to challenge the QSAR model developed based on the training set to assess the predictive effectiveness of the model which is not included in model generation. Sphere exclusion algorithm was used for creation of training and test sets. Sphere exclusion algorithm allows constructing training sets covering all descriptor space areas occupied by representative points. The higher the dissimilarity level, the smaller the training set is and the larger the test set is and vice versa.

Model Building**:** Data generated by k nearest neighbor molecular field analysis (kNN-MFA) in conjunction with stepwise (SW) forward-backward, simulated annealing (SA) and genetic algorithm (GA) variable selection methods with pIC50 activity field as dependent variable and descriptors as independent variable. Training and test set were selected and calculated for Unicolumn statistics (Table 3).

RESULTS AND DISCUSSION

Pharmacophore mapping shows hydrogen bond, hydrophobic bonding and aromatic hydrogen.

The common pharmacophoric features were identified by Pharmacophore mapping, three pharmacophoric sites were found to be hydrogen bond acceptor and other two were hydrogen bond donor. Pharmacophoric feature is shown by color coding. Green color shows Hydrogen bonding donor

while red color shows Hydrogen bonding acceptor. The functional groups which show pharmacophoric features were -NH Hydrogen bonding donor (HBD), -O Hydrogen bonding acceptor and S- Hydrogen bonding acceptor.

The docking is done among protein (pdb 3OLE), ligands and reference compound (Vildagliptin). Docking studies help in checking the interaction between protein and the ligands. Docking study showed that ligands 1 oxygen bind with His 740 of DPP-IV enzyme. The histamine is the selective target for inhibition of DPP-IV enzyme. Chemically histamine is the imidazole ring containing amino acid. The hydrophobic interaction between ligand and 3OLE as Tyr 547, Trp 629, Asn 710, Gly 741, Asp 739, His 740 and Ser 630.The docking score of the derivatives were 12b (-83.6954), 12c (-85.3678), 12e (-86.0359), 12k (-82.8949), 12m (-84.3965) and vildagliptin (-82.228). The docking score of the compound were equal to reference compound. The most active compound among derivatives was 12e with docking score - 86.0359.

Different training and test set of [(s)-γ-(arylamino)prolyl] thiazolidine derivatives were constructed using sphere exclusion. Training and test set were selected if they follow the Unicolumn statistics, i.e., maximum of the test is less than maximum of training set and minimum of the test set is greater than of training set, which is required for further QSAR analysis shown in table 3.

K-Nearest neighbor molecular field analysis (kNN-MFA) was applied using stepwise (SW) and, simulated annealing (SA) approaches for building QSAR models. Results of models developed by SW-kNN MFA and SA-kNN MFA using sphere exclusion methods. Significant QSAR model generated is shown in table 4.

Statistical measures used are shown in table 4 to correlate biological activity and molecular descriptors. Data fitness plot for model is shown in fig 6. Result of the observed and predicted biological activity for the training and test compounds for the Model is shown in table 5. From the plot it can be seen that kNN-MFA model is able to predict the activity of training set quite well (all points are close to regression line) as well as external. Sphere exclusion (SE) algorithm and random selection methods were used for constructing training and test sets. kNN-MFA methodology with stepwise (SW), and simulated annealing (SA) was used for building the QSAR models and alignment molecule with descriptor shown in fig 7.

Plot provided further understanding of the relationship between structural features of [(s)-γ-(arylamino)prolyl] thiazolidine derivatives and their activities which should be applicable to design newer potential as dipeptidyl peptidase IV (DPP IV) inhibitors.

Table 3: Uni-Column Statistics for Model 1 for training and test set activity.

Column Name	Average	Max	Min	Std Dev	Sum
Training set	7.5188	8.0757	6.8326	0.3872	82.7067
Test set	7.4813	7.6179	7.3448	0.1931	14.9627

Table 4: Result of kNN-MFA study using sphere exclusion selection method

S. No.	Dissimilarity value	Test set	MODEL 1 SW-kNN MFA		MODEL 2 SA-kNN MFA	
			q2	Predr2	q2	Predr2
1	9.22	12b, 12f, 12g	**0.6357**	**0.9744**	**0.8470**	**0.6741**

The most significant model is + Model showed that steric and electrostatic interactions play important role in determining DPP IV inhibitory activity Among several 3D QSAR model, two models 1, 2 with good statistical values were selected. The dissimilarity value in the model is 9.22 at which three test compounds were selected 12b, 12f, 12g and rest were in training set. It is necessary that the proposed models should have both the statistical quality as well as good predictive power therefore all the expressions were tested for internal and external validation. Both the validation put forward decision making input for selection of QSAR models.

Model 1: The model 1 was performed by stepwise method in Vlife. On model 1 significant activity with good correlation coefficient (0.65) and internal predictivity (0.97) is shown. In model electronic parameter E_319 4.2462 10.0000 is positive which shows that the electron withdrawing groups increases the biological activity.

Model 2: The model 2 was performed by simulated annealing method in Vlife. In model 2 significant activities with good correlation coefficient (0.84) and internal predictivity (0.67) is shown. The electrostatic parameter were E_328 -0.0113 -0.0085 suggesting that electron donating groups increases the biological activity near to the aromatic ring, E_249 7.4087 10.0000 shows that electron withdrawing groups increases potency on adding opposite to aromatic ring. Conclusion coming out from the model 2 is that both electron withdrawing and donating groups are responsible for increasing the biological activity. The steric factor S_403 0.0965 0.1603 and S_381 0.1372 0.3259 both were positive suggesting to increase the bulky groups near to the aromatic ring. The descriptors were shown in figure 7.

Model 1

kNN Method
Training Set Size = 10
Test Set Size = 3
Selected Descriptors:
Statistics:

k Nearest Neighbour	4
n	10
Degree of freedom	8
q2	0.6357
q2_se	0.2416
Predr2	0.9744
pred_r2se	0.0372

Descriptor Range:
E_319 4.2462 10.0000

Model 2

kNN Method
Training Set Size = 10
Test Set Size = 3
Selected Descriptors:
Statistics:

k Nearest Neighbour	5
n	10
Degree of freedom	4
q2	0.8470
q2_se	0.1565
Predr2	0.6741
pred_r2se	0.1326

Descriptor Range:
E_328 -0.0113 -0.0085
E_249 7.4087 10.0000
S_403 0.0965 0.1603
S_381 0.1372 0.3259
E_248 -9.8052 4.4554

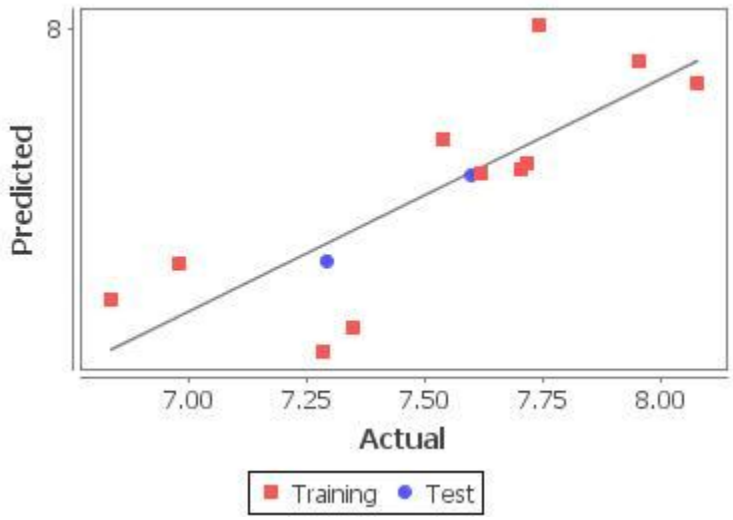


Figure 6: Graphical fitness plot between actual and predicted activity values for DPP-VI of model 2

Table 5: Actual and predicted biological activity for Training set and test set of model 2.

S. No	Compound	Actual	Predicted	
			SW-KNN MFA	SA-KNN MFA
1	12a	6.833	7.23078	7.23235
2	12b	7.618	7.5719	7.43524
3	12c	7.598	7.58774	7.57408
4	12d	7.717	7.61886	7.79945
5	12e	7.281	7.06946	7.15829
6	12f	7.345	7.32768	7.39111
7	12g	7.29	7.15029	7.11056
8	12h	6.979	7.30463	7.30777
9	12i	7.538	7.68392	7.66113
10	12j	7.701	7.60103	7.54905
11	12k	7.74	8.01315	7.90784
12	12l	7.955	7.90638	8.02407
13	12m	8.076	7.84622	7.94361

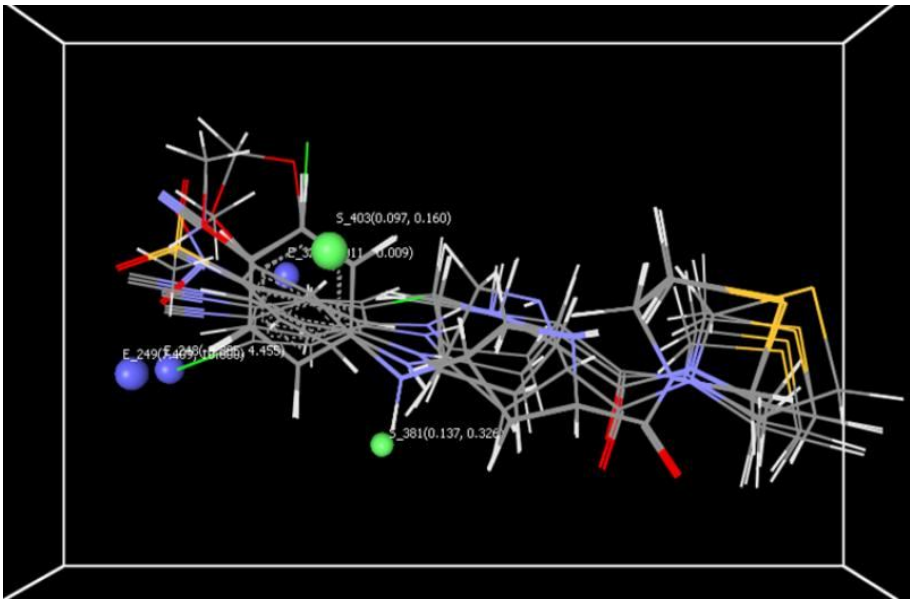


Fig 7: Showing 3D-Allignment of molecules and descriptor of model by wire frame model 2.

CONCLUSION

Pharmacophoric mapping, docking and QSAR were helpful in designing of potent derivatives. The common pharmacophoric features were identified by Pharmacophore mapping. The functional groups which show pharmacophoric features were -NH Hydrogen bonding donor (HBD), -O Hydrogen bonding acceptor and S- Hydrogen bonding acceptorBy the help of docking study interaction between the protein and ligand is checked. Indicated interaction unbound His 740 is essential for the inhibition of DPP-IV enzyme. Significant models were generated in sphere exclusion data selection method. Model developed to predict the structural features of [(s)-γ-(arylamino)prolyl] thiazolidine derivatives to inhibit dipeptidyl peptidase IV reveals useful information about the structural features requirement for the molecule. kNN-MFA models show that positive range in steric descriptors indicates bulky substituents group is preferred in that region and electronic parameter are positive to negative indicates both electron withdrawing and electron donating groups were preferred to increase the potency. On the basis of electrostatic and steric descriptor potential contributions to the developed model in this work is useful in describing QSAR of [(s)-γ-(arylamino)prolyl] thiazolidine derivatives as dipeptidyl peptidase IV (DPP IV) inhibitory activity and can be employed to design new derivatives with potent inhibitory activity.

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