

3D QSAR and Pharmacophore Identification of Heteroaryl piperazine-Substituted l-Prolylthiazolidines as Dipeptidyl Peptidase-4 Inhibitors

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ABSTRACT: This research article focuses on 3D QSAR, pharmacophore identification of heteroaryl piperazine-substituted l-prolylthiazolidines as dipeptidyl peptidase-4 inhibitors to identify the structural requirement for DPP-4 inhibition for the development of novel potent DPP4 inhibitors.

KEYWORDS: 3DQSAR, Pharmacophore, DPP-4 inhibitors.

Introduction

Diabetes mellitus is chronic disorder having high rate of mortality. The currently available anti diabetic drugs target either insulin resistance (metformin, glitazones), or insulin deficiency (sulfonylureas, glinides) but leading to shortfalls in medication. Dipeptidyl peptidase-4 is promising target for development of novel antidiabetic agents. The current advances in computational chemistry and bioinformatics the discovery of selective and safer drugs can be carried out in shorter time frame and with reduced cost. The X ray structure of DPP-4 shows 766-amino acid belonging to prolyl oligopeptidase family containing major three parts acytoplasmic tail, a transmembrane region and an extracellular part. The binding pocket of DPP-4 is very hydrophobic and is composed of the side chains, Tyr631, Val656, Trp662, Tyr666 and Val711 and aromatic side chains for binding with small molecules through pi-stacking interactions^[1-5]. QSAR analysis is utilised to correlate the physiochemical parameters with the biological activities. 3D QSAR methodologies are alignment dependent methods. Pharmacophore is defined as set of three dimensional features that are necessary for bioactive Ligands, pharmacophore identification plays vital role in development of potent and selective drugs. Pharmacophore modelling is process to identify the pharmacophore using alignment and distance geometry calculations^[5-10]. Here we report the 3DQSAR and pharmacophore identification on the heteroaryl piperazine-substituted l-prolylthiazolidines as dipeptidyl peptidase-4 inhibitors.

Experimental

Selection of data set

The data set for the present study was selected from the literature reported by Akahoshi et al^[5].

Ligand Preparation

The structure of 4-(4-phenylpiperazin-1-yl)pyrrolidin-2-yl(1,3-thiazolidin-3-yl) methanone was used as the template to built the molecules in the dataset in builder module of Vlife MDS 4.3, these ligands were further optimized by Merck molecular force field.

Molecular alignment

The alignment of molecules are important criteria for the 3D QSAR studies, the molecules of the dataset were aligned by the template based technique, using 4-(piperazin-1-yl)pyrrolidin-2-yl(1,3-thiazolidin-3-yl) me-thanone as a template for alignment of the molecules. The alignment of all the molecules on the template is shown in Figure 1.

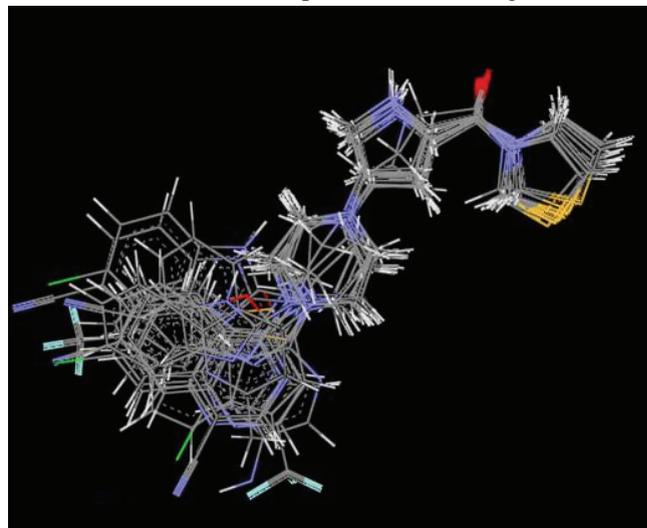


Fig. 1 Figure showing alignment of molecules.

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Descriptor Calculation

The hydrophilic, steric and electrostatic interaction energies of the molecules under study were computed using a methyl probe of charge +1 using QSAR module of the V Life MDS 4.3.

Data Set

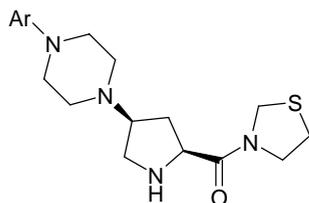
The dataset was divided into a training set and test set using the random selection method for generation of the training and test set data. The inhibitory constant (k_i) values were used for the present 3D-QSAR study.

Full Search Multiple Linear Regression Method

A relationship between independent and dependent variables (3D) fields and biological activities, respectively) were determined statistically using regression analysis.

Activity prediction

The generated QSAR models were selected on the basis of various regression parameters, and models which are having r^2 above 0.7 were checked for their external predictivity. The predicted values for DPP-4 Inhibitory activity are shown in Table 1.

Table 1 Table showing the molecules under study.

Sr no	Ar	Observed Activity	Predicted Activity
1.		0.92	0.93
2.		0.61	0.62
3.		0.73	0.8
4.		0.51	0.58
5.		2.2	2.5

6.		0.95	1.2
7.		0.56	0.61
8.		0.37	0.42
9.		0.61	0.70
10.		1.6	1.9
11.		0.80	0.91
12.		0.59	0.60
13.		0.39	0.45
14.		1.2	1.5
15.		0.50	0.52
16.		0.55	0.56
17.		0.42	0.41

Pharmacophore modeling

Pharmacophore modeling was also carried out in Vlife MDS 4.3 using Mol sig module. A pharmacophore model is a set of three dimensional features that are necessary for bioactive ligands. The minimum number of pharmacophore features generated for an alignment is taken 4 and tolerance is kept to 10 Å. The max distance allowed between two features is kept to 10 Å.

Results and Discussion

Results

The data set was randomly divided in to the training set (11 molecules) and test set (06 molecules). Different set of equations were generated but two models were selected on the basis of r^2 , q^2 , pred r^2 , F and p values (table 2).

Table 2 Table showing the selected QSAR equations along with statistical parameters employed for model selection.

Model No.	QSAR model	N	r^2	q^2	F value	Pred r^2
A	$K_i = 0.0103 + 0.1702 \cdot E_{290} - 0.1371 \cdot S_{249}$ (± 0.0330) (± 0.0516)	17	0.94	0.89	21	0.80

Discussion

Interpretation of QSAR Model

The model 3D QSAR model A was selected and which describes the structural features which are contributing towards the DPP-4 inhibitory activity of heteroaryl piperazine-substituted 1-prolylthiazolidines derivatives. The dataset under study were randomly classified in to training set of 11 molecules and test set of 06 molecules. The model was selected on basis of r^2 , q^2 , pred r^2 , F and p values. The r^2 value for model A was 0.9435 compared to that of model B 0.8523. The F test and p significance values were considered for the selection of model as shown in table 2. The steric interaction fields represented in green lattice points at S_249 is contributing negatively which shows substitution of bulkier groups for long chain systems could decrease the activity and substitution of smaller groups at aryl of heteroaryl moiety could results in to the active compounds as shown in figure 2 and 3. The electrostatic

interaction shown by the blue lattice point at E_290 is contributing positivity which indicates substitution involving the electron with drawing groups on aryl ring will increase the activity of molecules.

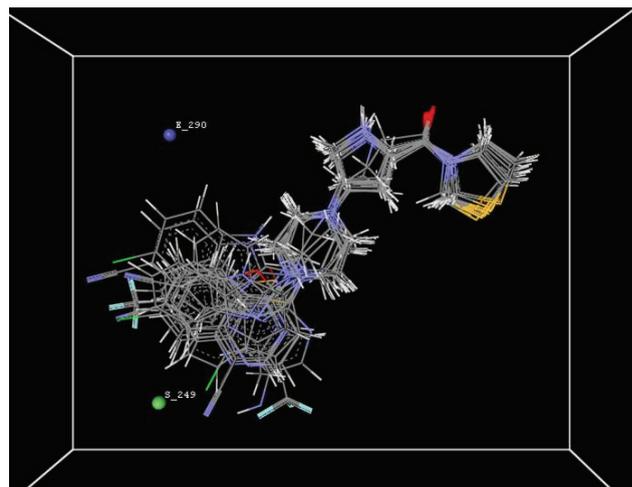


Fig. 2 Figure showing field point of selected QSAR model A.

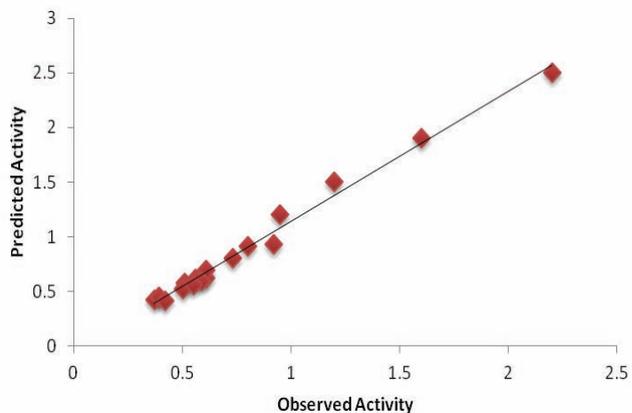


Fig. 3 Figure showing correlation plot for selected QSAR model.

Pharmacophore identification studies

The pharmacophore identification studies indicated the significance of positive ionisable, hydrogen bond donor and aliphatic features for DPP-4 inhibitory activity of heteroaryl piperazine-substituted 1-prolylthiazolidines derivatives. The two positively ionisable groups are must be 3.707 Å apart from each other while the distance between aliphatic and hydrogen bond donor and aliphatic and positively ionisable is 6.892 Å and 6.905 Å respectively for maximum DPP-4 inhibition as shown in figure 4 and 5.

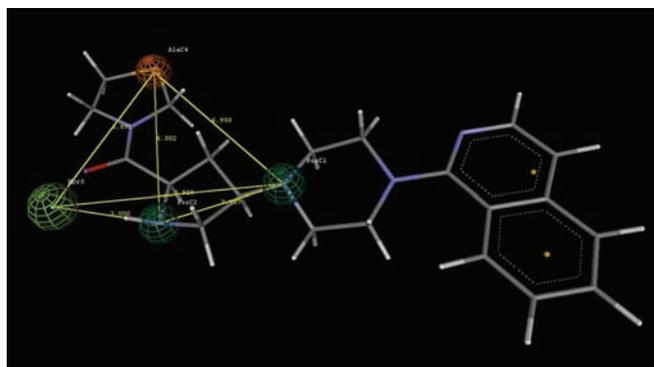


Fig. 4 Figure showing Pharmacophore modelling of molecules under study.

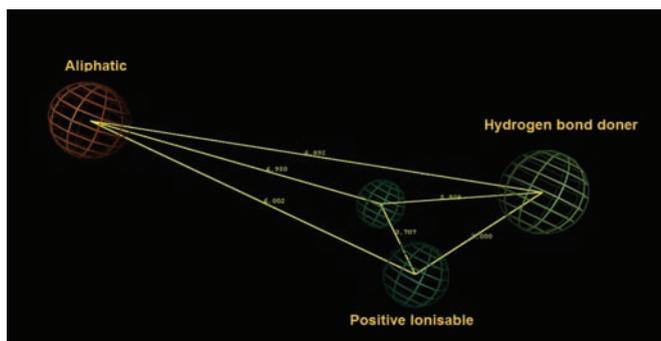


Fig. 5 Figure showing selected pharmacophoric hypothesis.

Conclusion

The 3D QSAR model generated shows the importance of substitution of smaller electron withdrawing groups on the aromatic rings in heteroaryl piperazine-substituted 1-prolylthiazolidines which are validated in pharmacophore identification, So QSAR model and pharmacophoric hypothesis generated can be used for further optimization

of DPP-4 inhibitors with high degree of selectivity and specificity.

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