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3D QSAR and Pharmacophore Identification Studies of Some Factor VIIa Inhibitors

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Abstract

3D QSAR and pharmacophore identification studies plays vital role in development of new potent NCE's. Various Coagulation factors are emerging target for the anticoagulant drug design. Here we report 3D QSAR and pharmacophore identification studies on 50 reported factor VIIa inhibitors. The QSAR equation and pharmacophore identification yielded that the presence of electron with drawing groups are important for factor VIIa inhibition.

Key words: 3D QSAR, Pharmacophore, Factor VIIa, Vlife MDS 3.5

INTRODUCTION

Haemostasis is a physiological response to any injury which results in the formation of a plug which prevents blood loss. In normal physiological condition, blood coagulation in control by the clotting factors and their natural inhibitors. The pathologic thrombosis occurs when the natural anticoagulants and fibrinolytic systems are fails. The factor VIIa triggers the whole coagulation process and inhibition of coagulation process in the early stages can be achieved by inhibition of factor VIIa/TF complex. In recent years the various scientist are targeted factor VIIa/ TF complex and developed various potent inhibitors[1-3]. The quantitative structure activity relationship can be utilised for correlating the structural properties with biological activities, which can give a platform for the optimization of previously reported inhibitors. Pharmacophore modelling is carried out to find out the optimum structural features which are required for that particular activity[4-9]. Here we report Pharmacophore identification and 3D-QSAR studies using PLS method on a training set of 40 derivatives as factor VIIa inhibitors, so the model which is investigated in this study will be useful for development of more potent factor VIIa inhibitors.

Computational details

Dataset

The reported data set of factor VIIa inhibitors by Shrader *et al*[10] were selected for the present study (Table 1). The data set is further divided in to the training set of 40 molecules and test set of 10 molecules by random selection method.

MATERIALS AND METHODS

Ligand Preparation

The benzimdazole nucleus was used as template to build the molecules in builder module of V Life MDS 3.5. All the drawn structures were minimized using MMFF with distance dependant dielectric function and energy gradient of 0.001 kcal/mol A^0.

Molecular alignment

The molecules of the dataset (Table 1) were aligned by the template based technique,

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on stable conformation of the most active molecule in data set. The alignment of all the molecules on the template is shown in Figure 1.

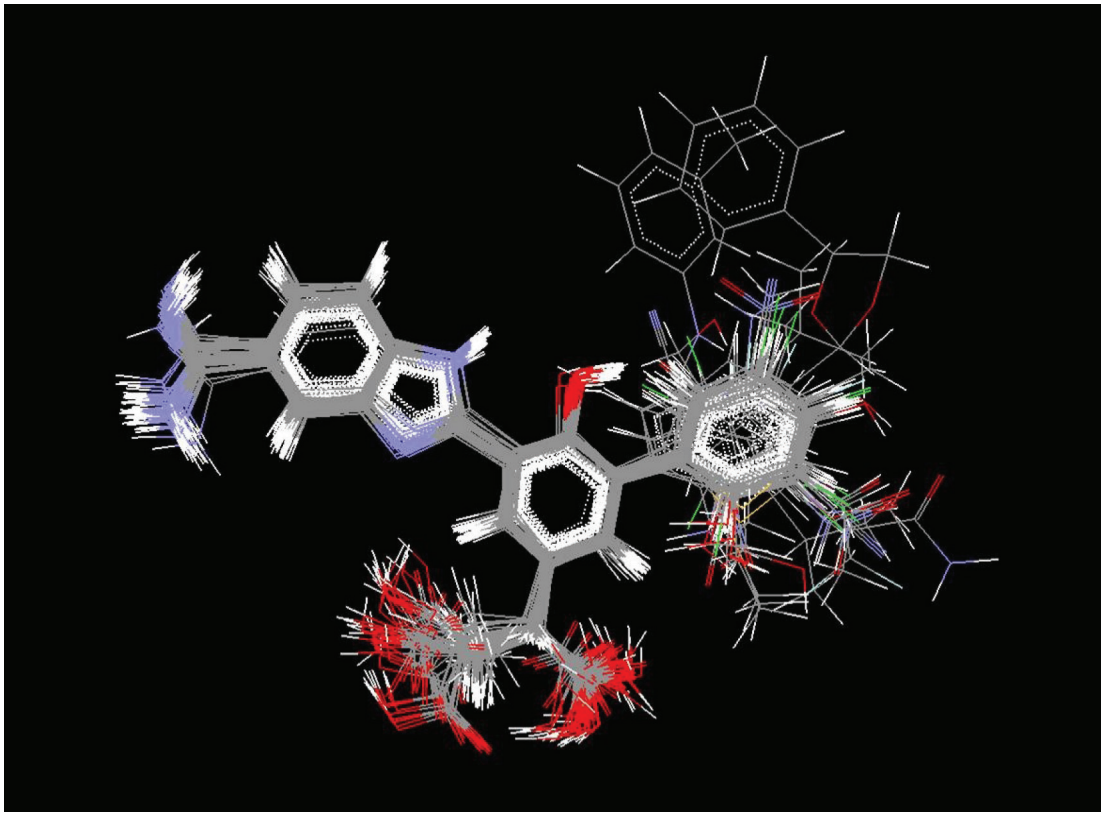


Figure 1. Crude drugs of the selected formula: *non tai yak* (A), *krajai* (B), *phaya fai* (C), and *mak teak* (D).

Descriptor Calculation

The descriptors calculation is carried out by generation of a common rectangular grid around the molecules. The hydrophilic, steric and electrostatic interaction energies which are computed at the lattice points of the grid using a methyl probe of charge +1.

3D QSAR studies using Partial least squares regression

A relationship between independent and dependent variables (3D fields and biological activities, respectively) were determined statistically using PLS analysis. Thus models having correlation coefficient above 0.7 were used to check the external predictivity while the significance of the model was decided on the basis of F value. Models showing q^2 below 0.6 were discarded. The selected models are shown in Table 2.

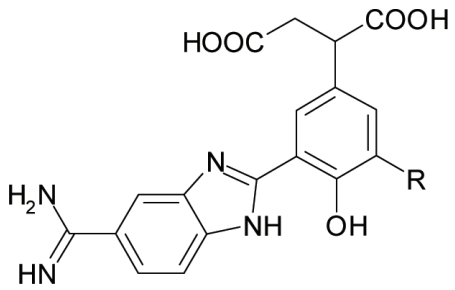
Pharmacophore modelling

Pharmacophore modelling was carried out using the mol sign module of Vlife MDS 3.5 software. The software was set to generate minimum 4 pharmacophoric features obtained keeping the tolerance limit at 10 A^0.

RESULTS

In the present study, 40 molecules were used in the training set (Table 1) to derive 3D QSAR models. To evaluate the predictive ability of generated 3D-QSAR models, and test set of 10 molecules with regularly distributed biological activities was used (Table 1).

Table 1. Table showing molecules under study



Sr. No.	R	Observed Activity	Predicted activity
1.	Phenyl	0.074	0.087
2.	2-Hydroxy-5-fluorophenyl	0.004	0.003
3.	2-Hydroxy-5-chlorophenyl	0.0054	0.008
4.	2-Hydroxy-5-nitrophenyl	0.006	-0.004
5.	2-Hydroxy-5-aminophenyl	0.01	0.083
6.	2-Hydroxy-5-cyanophenyl	0.012	-0.003
7.	2-Hydroxyphenyl	0.013	0.024
8.	2-Hydroxy-3-bromo-5-chlorophenyl	0.009	0.031
9.	2-Hydroxy-3,5-dichlorophenyl	0.014	-0.036
10.	2-Hydroxy-4,6-dichlorophenyl	0.025	0.041
11.	3-(Hydroxymethyl)phenyl	0.021	-0.038
12.	3-Nitrophenyl	0.022	-0.047
13.	2-Nitrophenyl	0.22	0.297
14.	3,5-Dichlorophenyl	0.027	-0.004
15.	3,5-Dimethylphenyl	0.029	0.023
16.	3-Acetylphenyl	0.033	-0.024
17.	3-Aminophenyl	0.036	0.002
18.	3-Methylphenyl	0.038	0.082
19.	N-(3-Methylphenyl)acetamide	0.054	0.285
20.	2-Thiomethylphenyll	0.064	0.088
21.	3-Chlorophenyl	0.066	0.063
22.	3,5-Difluoropheny	0.068	0.007
23.	3-Isopropylphenyl	0.076	0.091
24.	3-Cyanophenyl	0.077	0.075
25.	3-Hydroxyphenyl	0.088	0.057
26.	5-Chlorothiophene	0.11	-0.198
27.	3-Acetamidylphenyl	0.11	0.172
28.	3-(Difluoromethoxy)phenyl	0.12	0.130
29.	2-Methoxyphenyl	0.12	0.182

Sr. No.	R	Observed Activity	Predicted activity
30.	3-Chloro-4-fluorophenyl	0.13	-0.147
31.	5-(Hydroxymethyl)thiophene	0.13	-0.115
32.	2-Fluorophenyl	0.13	0.123
33.	2,3,5-Trichlorophenyl	0.21	0.216
34.	2,5-Dichlorophenyl	0.25	-0.130
35.	2,3-Dichlorophenyl	0.27	0.256
36.	3,4-Phenyldioxolone	0.28	0.257
37.	2-Methoxy-5-cyanophenyl	0.28	0.280
38.	2-Methoxy-5-fluorophenyl	0.33	-0.300
39.	2-Aminophenyl	0.42	0.423
40.	4-Methylphenyl	0.42	0.465
41.	4-Chlorophenyl	0.44	-0.597
42.	2-Methylphenyl	0.5	0.582
43.	3-Pyridyl	0.55	0.571
44.	2-(Hydroxymethyl)phenyl	0.73	0.742
45.	3-(Aminomethyl)phenyl	0.78	0.808
46.	4-Hydroxyphenyl	0.88	0.810
47.	4-Methoxyphenyl	2.25	2.022
48.	2-Acetylphenyl	4	6.33
49.	H	6.4	6.04
50.	4-tert-Butylphenyl	16	16.1

Table 2. Table showing the selected PLS 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	Ki= 0.0143+1.0946 S_1254+ 0.1496 S_365-0.1418 E_806+ 0.0573 S_904+0.0791 E_1347	50	0.92	0.83	100	0.86

DISCUSSION

Interpretation of 3QSAR Model:

The QSAR model A selected on the basis of various statistical parameters which can give the optimum structural features of selected data set which is responsible for factor VIIa inhibition. S_1254, S_365, E_806, S_904 and E_1347 are the parameters which are responsible for the activity. The interaction energy at the grid point S_1254, S_904 and S_365 is positively contributing so the substitutation of favoring the steric interaction can yield increase in activity. Substitution of alkyl or the aromatic ring on the phenyl ring and on benzimidazole nucleus can increase the activity. The grid point E_806 is negatively contributing so substitutions of electron with drawing groups on the aromatic ring can results in more active molecules, while the interaction energy at grind point E_1347 is positively contributing so substitution of electron releasing groups are preferred in this region for increasing the anticoagulant activity (Figure 2 & 3).

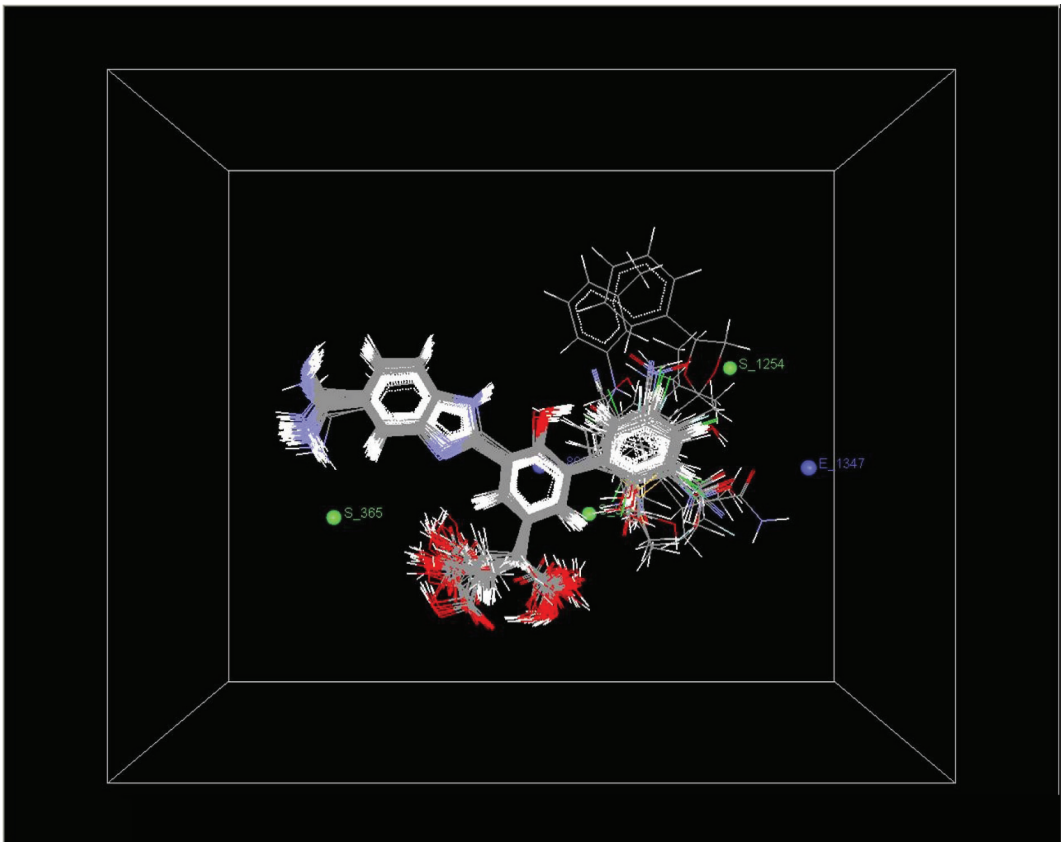


Figure 2. Figure showing field points of QSAR model A

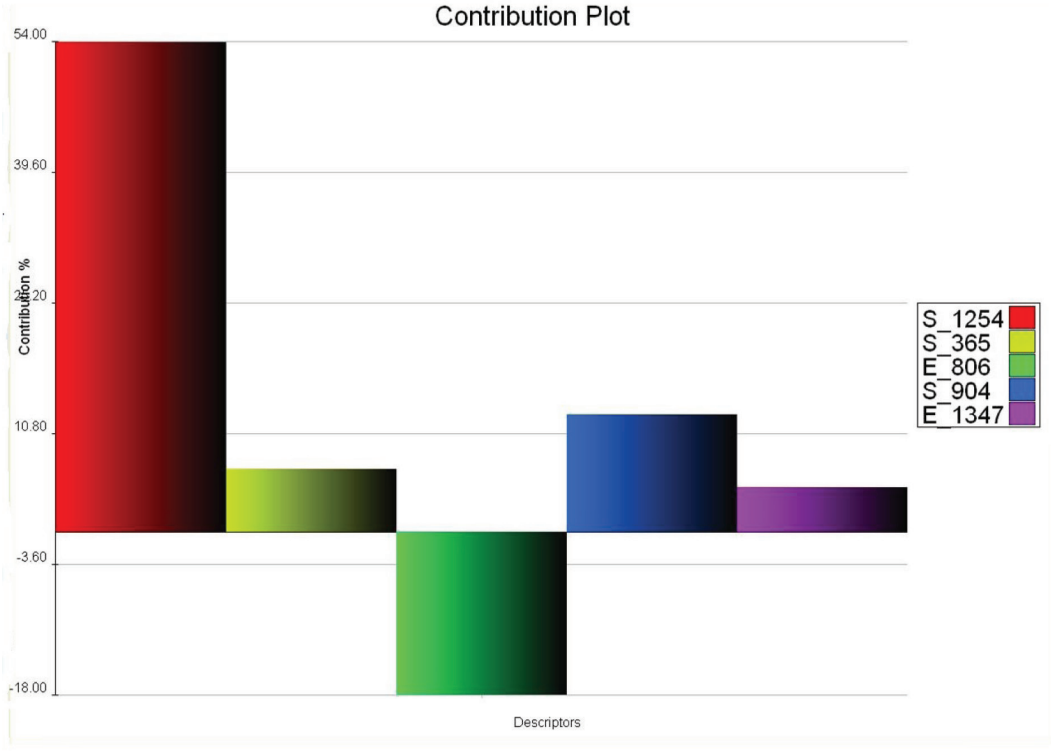


Figure 3. Figure showing contribution plot of QSAR model A

Pharmacophore identification studies using Vlife MDS 3.5:

The pharmacophoric hypothesis generated showed that Hydrogen bond donor, Negative ionizable, positive ionizable and aromatic are important pharmacophoric features for factor VIIa inhibition. The amidine group is contributing the positively ionizable property and carboxylic groups are contributing the negative ionizable property, which will be responsible for interacting with the acidic and basic amino acids in factor VIIa respectively. The aromatic and hydrogen bond donor are other two important features for activity. The hydroxyl group and secondary amino in benzimidazole are acting as hydrogen bond donor (Figure 4).

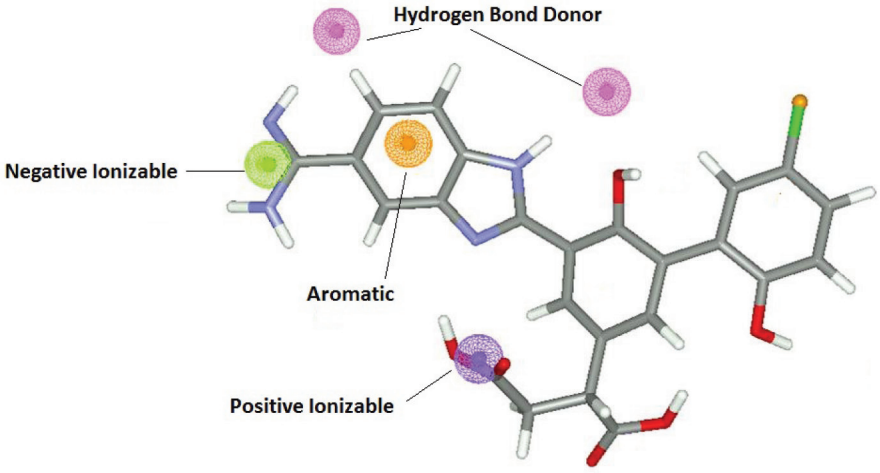


Figure 4. Figure showing selected pharmacophoric hypothesis

CONCLUSIONS

The current communication is an attempt to indentify and correlate the factor VIIa inhibition with the structural features of molecules under study which will be useful for further designing of more potent factor VIIa inhibitors prior to their synthesis.

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