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3D QSAR, Pharmacophore Identification of 5-Azaindole Derivatives as Factor VIIa Inhibitors

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ABSTRACT: The current manuscript deals with the three-dimensional quantitative structure-activity relationship (3D-QSAR) and pharmacophore identification studies on 33 substituted azaindole derivatives as factor VIIa inhibitors.

KEYWORDS: Factor VIIa; Anticoagulant; 3D QSAR; PLS.

Introduction

The factor VIIa plays an important role in the initiation of process of blood coagulation, and with association with tissue factor (TF), efficiently hydrolyzes the zymogen coagulation factors to the corresponding active serine protease forms, resulting in conversion of prothrombin to thrombin. Inhibition of factor VIIa can act as efficient tool in development of novel anticoagulant agents[1-5]. Quantitative structure-activity relationships (QSAR) represent an attempt to correlate 2D and 3D properties (descriptors) of compounds with biological activities. These physicochemical descriptors, which include parameters to account for hydrophobicity, topology, electronic properties, and steric effects, are determined empirically or, more recently, by computational methods. Activities used in QSAR include chemical measurements and biological assays. The QSAR relationship is expressed as a mathematical equation. QSAR based on multiple linear regressions are most commonly used, but many other statistical and mathematical methods may also be employed. The model derived from this investigation having good predictive ability, can be used to design more potent factor VIIA inhibitors[6-10].

Experimantal Procedure

Computational Details

A dataset of 33 compounds was taken from the published factor VIIa inhibitors by Riggs *et al.*,[11] their structures and their inhibitory activities are listed in Table 1. The whole dataset was randomly divided into a training set of 23 compounds and a test set 07 of compounds (asterisked molecules in Table 1). The training set was used to construct 3D-QSAR models and the test set was used for the models validation.

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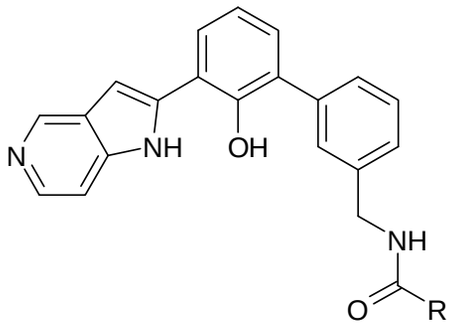
Table 1 Table showing Molecules under Study



Sr. No.	R	Observed activity	Predicted activity
1.	NH2	0.8	0.87
2.	Pentylamine	0.335	-0.23
3.	Phenylethylamine	0.27	0.16
4.	2-Thiphene-2yl-ethylamine	0.35	0.49
5.	Phenylamine	0.0615	0.04
6.	2-Fluoro-phenylamine	0.057	0.05
7.	3-Fluoro-phenylamine	0.13	0.26
8.	4-Fluoro-phenylamine	0.11	0.28
9.	2,6-Difluoro-phenylamine	0.033	0.04
10.	2,4-Difluoro-phenylamine	0.1	0.20
11.	3,4-Difluoro-phenylamine	0.33	0.34
12.	3,5-Difluoro-phenylamine	0.83	0.84

Table 1 *Contd…*

Sr. No.	R	Observed activity	Predicted activity
13.	2-Chloro-phenylamine	0.057	0.29
14.	2-Methoxy-phenylamine	0.047	0.03
15.	3-Methoxy-phenylamine	0.1	0.10
16.	4-Methoxy-phenylamine	0.088	-0.08
17.	2,4-Dimethoxy-phenylamine	0.028	0.03
18.	1-(3- Amino-phenyl)-ethanone	0.06	0.03
19.	1-(4- Amino-phenyl)-ethanone	0.19	0.10
20.	4-Amino-benzoic acid	0.058	0.05
21.	Thiophene-2-ylamine	0.16	0.20
22.	Thiophene-3-ylamine	0.13	0.29
23.	Pyridine-2-ylamine	2.7	2.55
24.	Pyridine-3-ylamine	0.155	0.27
25.	Pyrrolidine	17	16.1
26.	1-Methylpiperazine	130	130
27.	Toluene	2	2.07
28.	1,3-Difluoro-2-methyl-benzene	9.5	9.52
29.	2-Phenyl-ethanol	0.22	0.25
30.	2-Pyridin-3-yl-ethanol	0.61	0.72
31.	Phenyl-methanol	0.85	0.81
32.	Propyl-benzene	2.8	2.8
33.	*N*-Benzyl-hydroxylamine	0.072	0.07

Materials and Methods

The structure of azaindole was used as template to built the molecules in the dataset in Vlife MDS 3.5. All the structures was minimized using the standard Merck molecular force field (MMFF) with distance dependant dielectric function and energy gradient of 0.001 kcal/mol A^0.

Molecular Alignment

The molecules of the dataset were aligned by the template based technique, using common structure of azaindole. The alignment of all the molecules on the template is shown in Figure. 1.

Descriptor Calculation

The descriptors are noting but 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 regression analysis. Linear regression is achieved by fitting a best-fit straight line to the data using the least squares method. The quality of fit for a regression equation was assessed relative to its correlation coefficient and standard deviation. The F value represents the level of statistical significance of the regression. 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. (Figure 2).

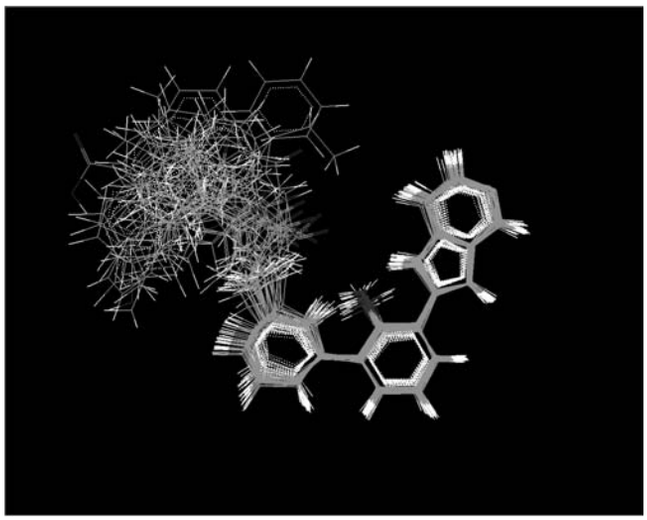


Fig. 1 Figure showing the alignment of molecules.

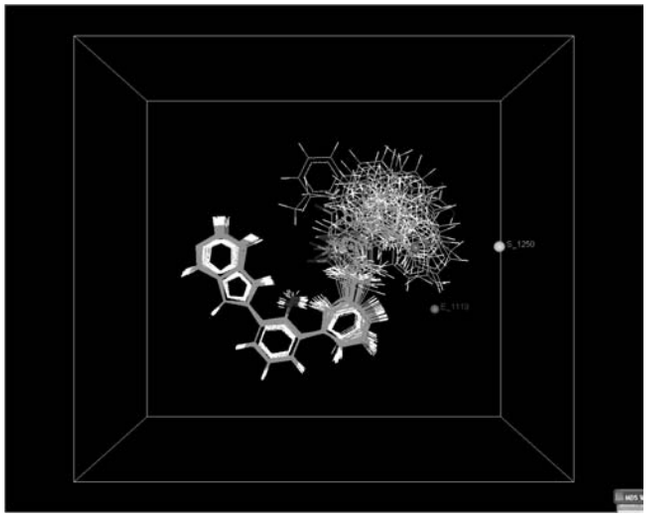


Fig. 2 Figure showing field points of QSAR model A.

Pharmacophore Modeling

Pharmacophore modeling was carried out using the mole sign module of Vlife MDS 3.5 software. Series of factor VIIa inhibitors were first aligned on the most active conformation. The software was set to generate minimum 4 pharmacophoric features obtained keeping the tolerance limit at 10 A^0

Results and Discussion

In the present study, 26 molecules were used in the training set (Table 1) to derive 3D QSAR models with the number of field grid points being not more than five per model. To evaluate the predictive ability of generated 3D-QSAR models, and test set of 07 molecules with regularly distributed biological activities was used (Table 1). On successful run of PLS two models were selected they are shown in Table 2.

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 = 0.0196 + 20.5328 S_812 – 116.8130 S_811 + 6.8842 S_1250 – 0.4507 E_1119 – 0.0349 E_1032	33	0.99	0.85	110	0.91

Interpretation of 3QSAR Model

The structural requirements of azaindole analogs to act as factor VIIa inhibitor are obtained in the form of 3D descriptors of the model A. The r^2 value for model A was 0.9998 (Figure 2 and 3). Model A shows the first model which is selected on the basis of statistical coefficient like r^2 (0.9998) and Pred r^2 (0.8923). The contributing descriptor for model A are S_812, S_811, S_1250, E_1119, E_1032 which are nothing but the electrostatic and steric interaction at that lattice point. The electrostatic interaction at lattice point E_1119 and E_1032 are negatively contributing means substitution of electron withdrawing groups will be increasing the inhibitory potential of the molecules. Also the steric interaction at the lattice point S_811 is negatively contributing, so substation of smaller groups can increase activity. The steric interactions at the S_812 and S_1250 are positively contributing so substitution of bulkier groups in that region can increase the activity of the molecules.

Pharmacophore Identification Studies using Vlife MDS 3.5

A set of pharmacophore hypothesis was generated using the mole sign module of Vlife MDS 3.5 on the molecules understudy and each hypothesis was found to contain common features like hydrogen bond doner, hydrogen bond acceptor and aromatic. The pharmacophore hypothesis generated in Vlife MDS 3.5 (Figure 4) indicated that hydrogen bond donor and hydrogen bond acceptor and three aromatic features are required for factor VIIa inhibition. The phenolic hydroxyl group is important for hydrogen bond donation, while the pyridine nitrogen in required for hydrogen bond acceptance.

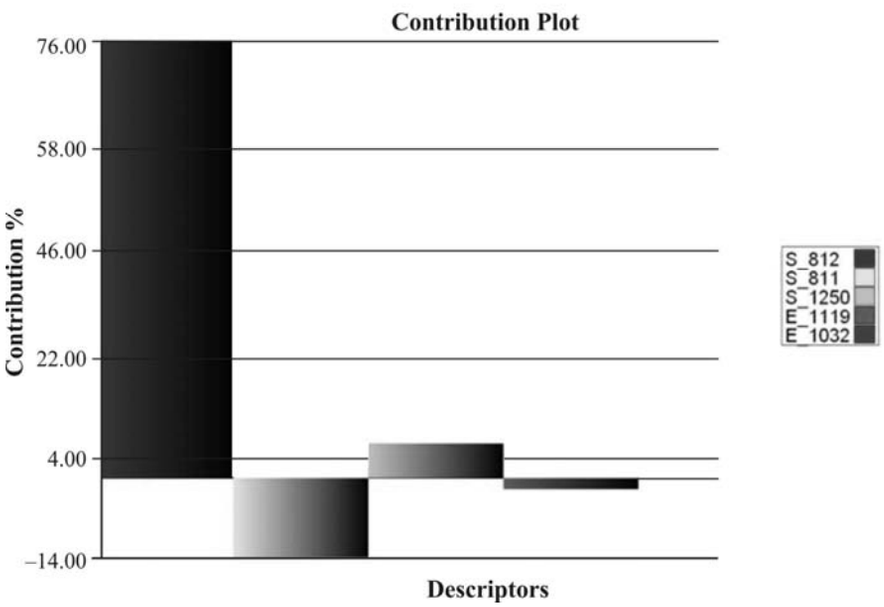


Fig. 3 Figure showing contribution plot of QSAR model A.

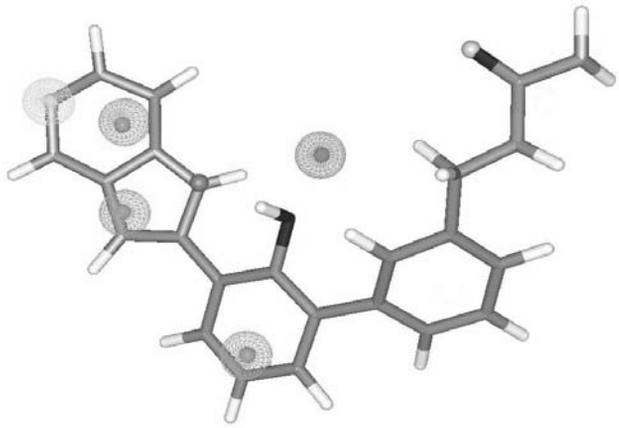


Fig. 4 Figure showing selected pharmacophoric hypothesis.

Conclusion

The present communication is an attempt to identify the requirement of azaindole for inhibition of factor VIIa. The pharmacophoric hypothesis indicated the importance of free hydroxyl group and heterocyclic nucleus. Thus the model derived from this study having good predictive ability, which could be useful for designing newer factor VIIa inhibitors.

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