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Research Article

QSAR ANALYSIS OF (S)-3-(2-(NAPHTHALENE-2-SULFONAMIDO)-3-OXOBUTYL) BENZIMIDAMIDE DERIVATIVES AS FACTOR XA INHIBITOR

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ABSTRACT

A dataset of (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives were tested for their inhibitory activities against the enzyme factor Xa ,thereby acting as anticoagulants .Quantitative structure activity relationship (QSAR) analysis was applied to 19 candidates of the (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives using a combination of various physicochemical, steric, electronic, and structural molecular descriptors. The most significant models as a calibration model for inhibitory activity of (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives were reported by using multiple linear regression(MLR).For predicting the inhibitory activity of this class of compound ,the stepwise regression method was used. With the leave one out (LOO) technique and statistical parameters , the best QSAR models were cross validated. The results obtained in the validation procedure shows high agreement between experimental and predicted inhibitory values, indicating the good quality of derived QSAR models.

Keywords: QSAR; Multiple Linear Regression; (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives; factor Xa.

INTRODUCTION

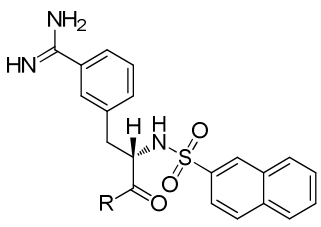
QSAR analysis helps in the rational search of molecules which are biological active. With the help of QSAR studies, one can estimate the characteristics of new chemical compounds without synthesizing and testing them. The above analysis is an attempt to get the relation between structural descriptors of compounds with the biological activities and physicochemical properties. This method included data collection, molecular descriptor selection, correlation model development, and finally model evaluation. QSAR studies have predictive ability and simultaneously provide deeper insight into mechanism of drug receptor interactions[1-3]. Thrombin is a serine protease responsible for blood coagulation. Since thrombin inhibitors appear to be effective in the treatment and prevention of thrombotic and embolic disorders, considerable attention has been focused on the structure and interactions of this enzyme. Therefore to evaluate the relative free energies of hydration and binding to thrombin for (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives were used[4]. Thrombin plays a key role in haemostasis by mediating conversion of fibrinogen to fibrin and activating platelets. Thrombin inhibitors prevent intravascular clot formations which cause many cardiovascular diseases such as myocardial infarction, deep vein thrombosis, and ischemic stroke. Some thrombin inhibitors (argatroban, heparin, etc.) are available but these agents are not orally active. Therefore, an orally active thrombin inhibitor would be useful in clinical practice. Most of the synthetic thrombin inhibitors reported before have a highly basic functional group like guanidine which interacts with Asp 189 (P_1 pocket) of thrombin and these highly basic functional groups cause low membrane permeability. Traditionally heparin and its analogues and warfarin are used for the prevention or treatment of thromboembolic diseases but they have many limitations for example it has a narrow therapeutic window and requires monitoring by lab testing[5]. This result in continuously growing thrombus during heparin therapy and clotting may be reactivated after heparin therapy has been discontinued. To overcome these limitations, development of other antithrombotic agents[6-12] started. Some of these newer anticoagulants are factor Xa inhibitors and direct thrombin inhibitors. Factor Xa is a member of the trypsin-like serine protease class of enzymes. A one-to-one binding of factors Xa and Va with calcium ions and phospholipid forms the prothrombinase complex which converts prothrombin to thrombin. Thrombin, in turn, converts fibrinogen to fibrin which polymerizes to form insoluble fibrin. Consequently, Factor Xa has emerged as an attractive target for the development of antithrombotic drugs[13].

MATERIALS AND METHODS

To develop a QSAR model, diverse set of data is needed. "A chemical descriptor is the final result of a logical and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number or the result of some standardized experiment."

DRAGON is an offline package developed by Roberto Todeschini and co-workers to calculate descriptors of all classes. In case when molecule contains more than 55 atoms as in some large molecules, DRAGON fails to compute it. In this event E-DRAGON, an online server can be brought in computation of descriptors[15-16]. Calculation of descriptors has been achieved using E-dragon. A set of (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives were used for MLR model generation. The analysis of matrix revealed those 5 descriptors for the development of MLR model. Table 2 represents the values of descriptors chosen for MLR model. Molecular properties were calculated using Chem. Bio 3D Ultra.

Table 1: The structures of the compounds and Ki values for factor Xa.



R= Substituent

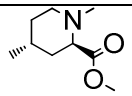
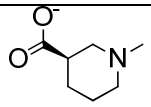
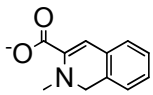
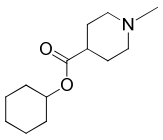
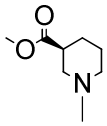
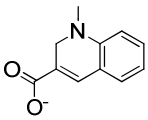
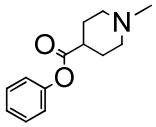
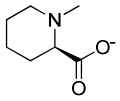
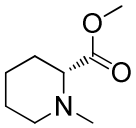
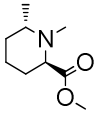
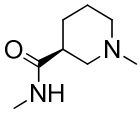
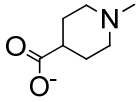
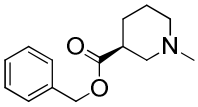
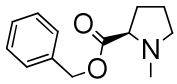
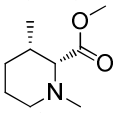
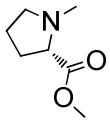
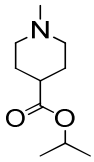
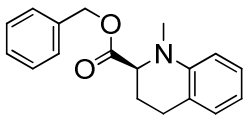
Compound	R	Ki	Compound	R	Ki
1		4.237	11		4.357
2		4.268	12		5.119
3		4.745	13		4.387
4		5.092	14		4.658
5		4.42	15		4.337
6		5.495	16		4.481
7		4.363	17		5.066
8		4.699	18		4.444
9		3.959	19		4.602
10		5.114			

Table 2: It shows values of molecular descriptors used in the regression analysis.

Compound	Sv	Torsion	Ui	PSA	ARR	1,4 VDW
1	43.99	27.91	4.524	142.65	0.415	61.08
2	43.9	-6.27	4.907	153.65	0.523	21.30
3	42.39	53.80	4.524	142.65	0.425	17.09
4	47.99	44.56	4.858	142.65	0.5	15.42
5	40.5	-0.04	4.524	153.65	0.436	14.99
6	43.99	27.35	4.524	142.65	0.415	9.17
7	40.5	50.91	4.524	153.65	0.436	21.76
8	47.99	9.52	4.858	142.65	0.5	13.16
9	40.8	0.88	4.524	142.65	0.436	10.69
10	53.59	-16.45	5.129	142.65	0.558	24.46
11	40.5	-1.27	4.524	153.65	0.436	22.68
12	49.79	50.12	4.524	142.65	0.37	10.24
13	43.9	18.31	4.907	153.65	0.523	39.51
14	41.97	-0.67	4.459	116.35	0.447	11.16
15	42.39	26.99	4.524	142.65	0.425	72.23
16	42.88	0.95	4.524	145.45	0.425	8.92
17	49.59	45.76	4.858	142.65	0.489	12.34
18	43.99	29.98	4.524	142.65	0.415	12.38
19	45.59	0.95	4.524	142.65	0.405	12.41

Graph Pad Instat 3.06 was used to design linear models. In this, descriptors were added and deleted stepwise to obtain linear model. Here, descriptor acts as input for the software Graph Pad Instat 3.06 and then the sequential addition method was implemented for selecting the descriptors for inhibitory effect of (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives based on lower values of interdependency. The best selected multiple linear regression specifications are represented in Table 3.When the number of descriptors are 5 or 6 times lesser than the number of molecules, then only MLR can be used. Therefore in this case, only 5 descriptors are used to build a good QSAR model in order to avoid a high chance of unintended correlations.

Table 3: It shows best MLR models for the prediction of antithrombotic activity

Model	Coefficient	Error	n	r	s	F
1	8.576	5.249	19	0.768	0.467	8.604
2	2.523	0.916	19	0.815	0.371	11.493

QSAR studies has been carried out with respect to 3 major components that is development of QSAR model, validation of model and utility of developed models. The crucial aspect of any QSAR analysis is validation[17].To check the statistical quality of resulting model, r, s and F are determined and are represented[18-20] in Table 3 .All these equations were obtained without any outliers that is with 19 candidates of (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives.

The following statistical parameters were calculated to test the validation of developed models; PRESS, SSY, S_{PRESS}, r^2_{CV} and r^2_{adj} (Table 4). The following equations are used to calculate above parameters.

$$PRESS=\Sigma (Y_{obs}- Y_{calc})^2 \quad (1)$$

$$SSY=\Sigma (Y_{obs}- Y_{mean})^2 \quad (2)$$

$$S_{PRESS}= \sqrt{PRESS\backslash n} \quad (3)$$

$$r^2_{cv} \text{ or } Q^2= \frac{1- PRESS}{SSY} \quad (4)$$

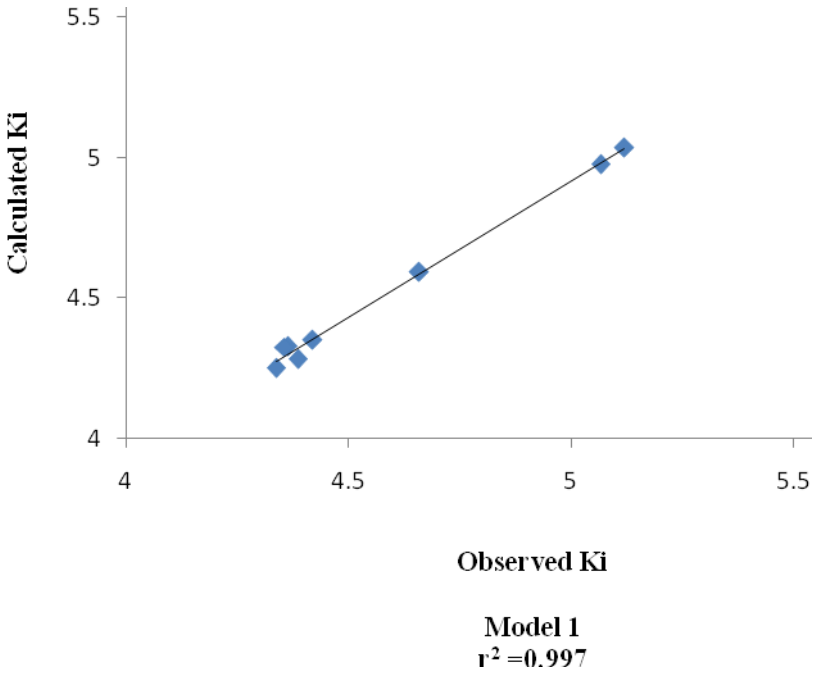
$$r^2_{adj}= 1- (r^2)[n-1/n-p-1] \quad (5)$$

Where, Y_{obs}, Y_{calc} and Y_{mean} are observed, calculated and mean values; *n*, number of compounds; *p*, number of independent parameters. PRESS is used for predicting sum of squares. To validate a regression model with respect to predictability, PRESS is utilized. The deviation of Y_{obs} from the actual Y value is called the prediction error. The sum of the squared prediction errors is known as PRESS value. The lesser PRESS value shows higher predictability of the model. If PRESS value is lesser than SSY then predictability of model is better than chance and it is statistically significant. With the help of PRESS value, r^2_{CV} statistic or r^2 cross validated can be calculated which shows the prediction ability of the model. Many a times, r^2_{CV} and r^2_{adj} are considered as a proof of the high predictability of QSAR models. If the values of these characteristic are >0.5 then the QSAR model has high predictive power, but the recent studies shows reverse of it[21]. If r^2_{CV} is low then it indicates low predictive power of model therefore LOO r^2_{CV} is the need of a model to have a high power of prediction. Although it is already proved that to have high predictive power of a model, large number of compound must be taken as data set. The minimum number of compound must not be less than five compounds. The values of binding affinity of various molecules for factor Xa were calculated in the model 1 and 2.Calculated data and observed data were found to be in good agreement. The cross validation parameters are shown in Table 4.

Table 4: It shows Cross validation parameters of Generated QSAR Models 1 and 2

Model	PRESS	SSY	PRESS/SSY	S_{PRESS}	r^2_{cv}	r^2_{adj}
1	1.270	2.771	0.458	0.260	0.541	0.231
2	1.475	3.999	0.368	0.278	0.607	0.334

The plots of linear regression predicted *versus* experimentally observed values of the (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives are shown in figure 1.



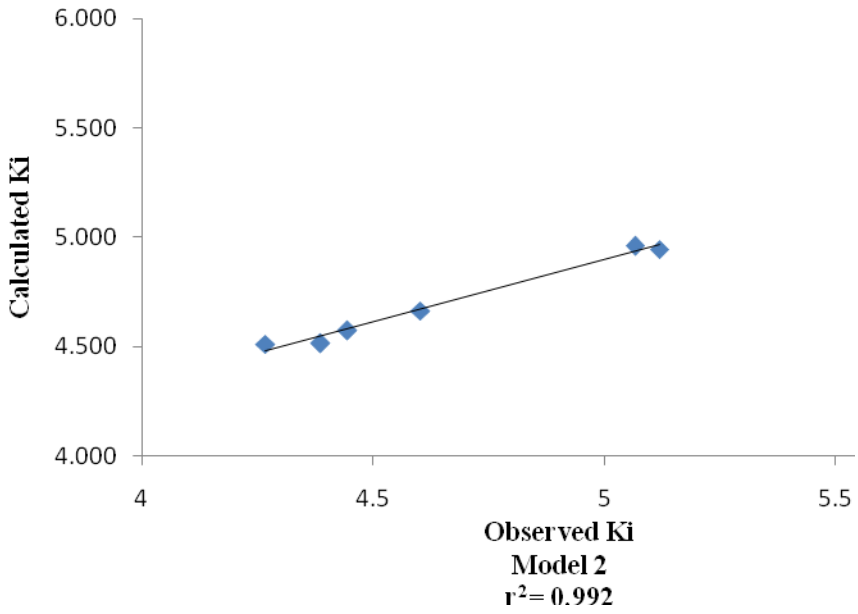


Fig. 1: It shows Plots of predicted versus experimentally observed inhibitory activity of (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives

Table 5: It shows Predicted Ki values of (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives Vs Experimental Ki values of Model 1

Model 1			
Compound	**Exp. Ki**	**Pred. Ki**	**Residual**
5	4.420	4.351	0.069
7	4.363	4.329	0.034
11	4.357	4.326	0.031
12	5.119	5.036	0.083
13	4.387	4.283	0.104
14	4.658	4.593	0.065
15	4.337	4.251	0.086
17	5.066	4.976	0.090

Table 6: It shows Predicted Ki values of (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives Vs Experimental Ki values of Model 2

Model 2			
Compound	**Exp. Ki**	**Pred. Ki**	**Residual**
2	4.268	4.512	-0.244
12	5.119	4.946	0.173
13	4.387	4.514	-0.127
17	5.066	4.961	0.105
18	4.444	4.574	-0.130
19	4.602	4.664	-0.062

RESULT AND DISCUSSION

In the first step of present study, different substituted (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamides were evaluated as factor Xa inhibitor as antithrombotic agents. The dataset includes set of 20 molecules with their binding affinities towards factor Xa. Determination of binding affinity has been performed in identical conditions and in the same laboratory which make this dataset compatible for the use of QSAR studies[14].The datasets including molecular structure and their binding affinity towards factor Xa in the form of Ki values is shown in Table 1.

CONCLUSION

From the above discussion, it has been concluded that (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide derivatives are effective factor Xa inhibitors. QSAR study have been performed to analyse the quantitative effects of the molecular structure of the (S)-3-(2-(naphthalene-2-sulfonamido)-3-oxobutyl)benzimidamide on their inhibitory activities. To predict the antithrombotic activities of above class of compounds, mathematical models were proposed. Statistical parameters were calculated to validate the models. From the proposed QSAR models, it has been observed that observed and calculated values shows high agreement. The good predictability of the model is further confirmed by low residual activity and high values of cross validated r^2. Plots of QSAR model 1 and 2 shows good r^2 values that is r^2 =0.997 and r^2 =0.992 respectively. It shows that models 1 and 2 can be successfully applied to predict the antithrombotic activity of this class of compounds.

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