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Bioorganic & Medicinal Chemistry 14 (2006) 319–325
Bioorganic & Medicinal Chemistry

QSAR studies of N_1-(5-chloro-2-pyridyl)-2-{[4-(alkyl methyl)benzoyl]amino}-5-chlorobenzamide analogs

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Received 22 June 2005; revised 22 July 2005; accepted 23 July 2005
Available online 4 November 2005

Abstract—Factor X_a has materialized as a key enzyme for the intervention of blood coagulation cascade and for the development of new antithrombotic agents. It is the lone enzyme that is responsible for the production of thrombin and is therefore an attractive target for the control of thrombus formation. The biological activities ($\log 1/IC_{50}$) of anthranilamide-based factor X_a inhibitors were quantitatively analyzed in terms of physicochemical parameters by the regression analysis. Structural requirements for maximal potency were derived from the results of a quantitative structure activity relationship analysis. The leave-one-out cross-validation method was used to judge the predictive power of final equations.

1. Introduction

Fatal damage is often caused by thrombotic events. Hence, numerous efforts have been made to synthesize antithrombotics, such as antiplatelet, anticoagulant, and thrombolytic agents. Thrombin plays a critical role in thrombosis, since it not only converts fibrinogen to fibrin for clot formation but also strongly induces platelet aggregation. The human factor X_a is a trypsin-like serine protease that serves a critical role in blood coagulation events.[1] The factor X_a combines with factor V_a and platelet phospholipid, as a result a prothrombinase complex is formed. This prothrombinase complex, in turn, initiates the splitting of prothrombin to form thrombin thereby setting in motion the final clotting process. Since it was calculated that a molecule of factor X_a could generate 138 molecules of thrombin,[2] inhibition of factor X_a may be more efficient than inactivation of thrombin in interrupting the blood coagulation system. The early factor X_a inhibitors, such as BABCH,[3] DABE,[4] and DX-9065a,[5], were mostly bisamidines. The poor pharmacokinetics, including low oral bioavailability, of these compounds led to the synthesis of a variety of monobenzamidines as factor X_a inhibitors in which the P1 amidino group is retained because it has been deemed critical for a strong binding with factor Xa. However, most mono-benzamidines still lack a desirable level of oral absorption to be developed as oral anticoagulants.[6–10] An amidine moiety on typical small molecule drug candidates is often associated with low oral bioavailability, short half-life, and rapid clearance. For this reason, anthranilamide-based factor X_a inhibitors were targetted and have been reported by several groups.[11–13] One of the leads of anthranilamide-based factor X_a inhibitors was found to be of low anticoagulant activity, which was partially attributed to the low hydrophilicity and high plasma protein binding.[14] In an effort to design more hydrophilic and less lipophilic factor X_a inhibitors, recently N_1-(5-chloro-2-pyridyl)-2-{[4-(alkyl methyl)benzoyl]amino}-5-chlorobenzamide (ABXa) analogs were synthesized by replacing the distal phenyl ring in the lead compound.[15]

In continuation of our research,[16–19] the present communication is an attempt to explore the quantitative structure–activity relationship (QSAR) of the analogs of ABXa. It is aimed at explaining the observed variance in biological activity as a function of various physicochemical parameters and predicts the best factor X_a inhibitory compound.

2. Computational methods

2.1. Data set

The physicochemical parameters, such as molar refractivity (MR) and lipophilicity ($Q\log P$) of the substituents,

Keywords: ABXa inhibitor; QSAR; Regression analysis; Cross-validation.
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0968-0896/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.bmc.2005.07.058

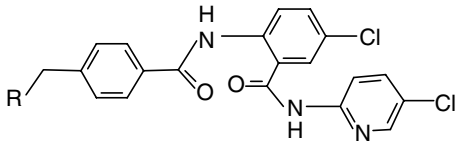


Figure 1. N_1-(5-Chloro-2-pyridyl)-2-{[4-(alkyl methyl)benzoyl]amino}-5-chlorobenzamide.

were calculated by Molecular Modeling Pro. of Chem Sw.[20]

2.2. Molecular structure building

A series of compounds tested for biological activity[15] was selected for the present study and the program of window Chem Software Inc. was used in modeling studies. The molecules were generated and the energy was minimized using Molecular Modeling Pro. The window version software[21] SPSS 10 was used in the regression analysis.

2.3. Building of QSAR models

QSAR technique[16–19] was applied to the analogs of ABXa that were varied at the 'R' position (Fig. 1). Appropriate descriptors or parameters for the compounds, $Q\log P$ and MR, were correlated to the observed inhibitory activity on factor X_a and were used as explanatory variables in the multiple regression analysis. The regression models are the QSAR molecular models that were used to predict and design a compound with the best possible inhibitory property.

2.4. Chemical descriptors

2.4.1. Lipophilicity parameter ($Q\log P$). The lipophilicity factor P ($Q\log P$) is the most widely used property where P is defined by a 1-octanol/water partition coefficient. All the $Q\log P$ values used were calculated as per the Bodor and Buchwald[22] method in Chem Sw.

2.4.2. Molar refractivity. This parameter gives a measure of the steric factors and bulkiness of the given base molecule with various substituents. It is the molar volume corrected by the refractive index and represents the size and polarizability of a fragment or molecule.[23]

Molar refractivity is given by:

$$\mathrm{MR} = \frac{(n^2-1)}{(n^2+2)} \times \frac{(\mathrm{MW})}{d},$$

where n is the refractive index, MW is the molecular weight, and d is the compound density.

2.5. Correlation analysis

Relationship between biological activity, expressed as $\log 1/\mathrm{IC}_{50}$, and the physicochemical parameters x_i ($Q\log P$ and MR) was analyzed statistically by fitting the data to correlation equations consisting of various combinations of these parameters.

Table 1. Activity and physicochemical properties of the ABXa analogs

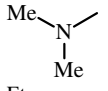
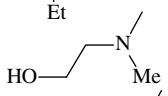
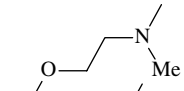
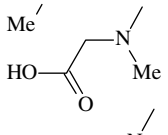
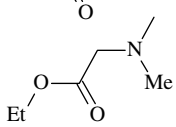
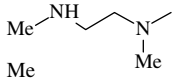
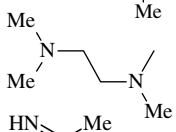
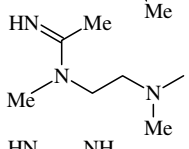
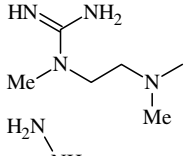
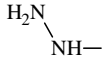
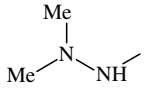
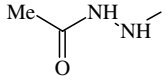
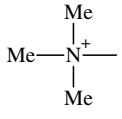
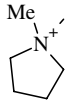
S.No	R	IC_{50} (nM)	Activity	$Q\log P$	MR
1		10	2.000	2.829	117.017
2		7	2.155	3.328	121.791
3		4	2.397	3.825	127.086
4		12	1.920	4.311	131.834
5		35	1.456	4.797	136.582
6[a]		82	1.086	3.105	133.378
7		53	1.276	3.606	138.129
8[a]		156	0.806	3.180	133.321
9[a]		176	0.754	4.165	142.838
10		6.8	2.167	3.699	139.810
11		6.9	2.161	4.197	145.105
12		1.1	2.958	3.405	151.831
13		2	2.699	1.807	150.630
14		40	1.397	1.725	120.194
15		0.9	3.045	2.720	129.988
16[a]		40	1.397	1.604	131.406
17[a]		0.8	3.096	4.439	129.190
18[a]		2.3	2.638	5.083	136.521
19		5.8	2.236	4.431	138.162

Table 1 (*continued*)

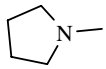
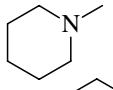
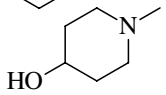
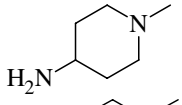
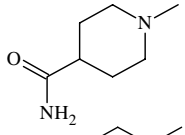
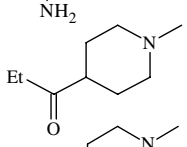
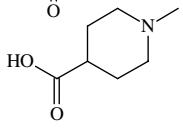
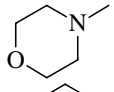
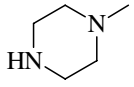
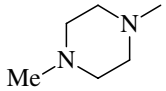
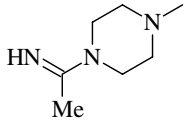
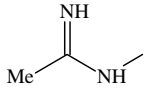
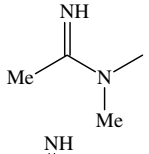
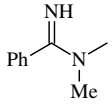
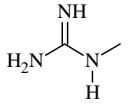
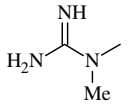
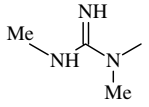
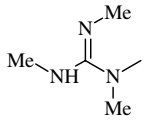
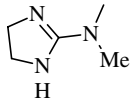
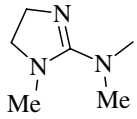
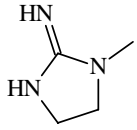
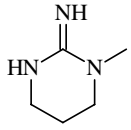
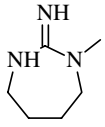
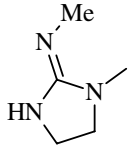
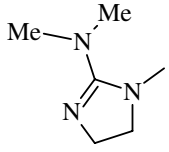
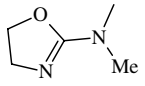
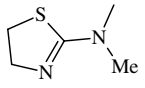
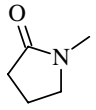
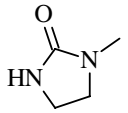
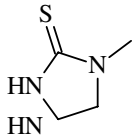
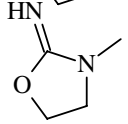
S.No	R	IC_{50} (nM)	Activity	$Q\log P$	MR
20		16	1.795	4.466	134.626
21		15	1.823	4.952	139.227
22[a]		136	0.866	3.744	140.810
23		15	1.823	3.842	142.468
24[a]		76	1.119	2.950	147.411
25[a]		171	0.767	5.290	154.984
26[a]		230	0.638	4.307	145.467
27[a]		140	0.853	3.276	136.160
28		17	1.769	3.372	137.841
29		15	1.823	3.868	143.136
30		5	2.301	3.076	149.862
31		3.6	2.443	2.534	128.517
32		0.9	3.045	3.033	133.812
33		11	1.958	4.582	153.985
34		1.4	2.853	0.937	127.316
35		1	3.000	1.436	132.611
36		0.7	3.154	1.935	137.386

Table 1 (*continued*)

S.No	R	IC_{50} (nM)	Activity	$Q\log P$	MR
37		0.8	3.096	2.427	142.282
38		2	2.699	2.097	140.313
39		0.3	3.522	2.592	145.608
40		1.5	2.823	1.603	135.417
41		3.8	2.420	2.087	140.282
42		6.3	2.200	2.574	144.926
43		3.5	2.455	2.096	140.313
44		1.3	2.886	2.592	145.608
45		1.5	2.823	1.997	138.363
46		10	2.000	3.755	144.807
47[a]		552	0.258	3.094	134.252
48[a]		30	1.522	1.503	133.359
49		35	1.455	2.555	141.350
50		0.2	3.699	1.504	133.467

[a] Outliers.

$$\log 1/IC_{50} = \sum a_i x_i,$$

where a_i is the correlation coefficient and x_i is the physicochemical parameter.

Statistical optimization is used to propose the best correlation model. The constant and the correlation coefficient, a_i for each term, were determined by the least-squares method.

3. Results and discussions

The biological activity data and the physicochemical properties $Q\log P$ and MR of the ABXa analogs are given in Table 1. The data from Table 1 were subjected to regression analysis. Correlation matrix was generated with 50 analogs. The correlation terms involved in the correlation matrix (Table 2) indicate the extent of co-linearity. The term close to 1 indicates high co-linearity, while the value below 0.5 indicates that no co-linearity exists between the two parameters. The perusal of correlation matrix (Table 3) indicates that MR and $Q\log P$ are the predicted parameters. In the initial stage, mono-parametric QSAR equations were generated with $Q\log P$. It is interesting to record that R^2_A(adjusted) values take into account the adjustment of %EV. Therefore, if a variable is added which does not contribute its fair share, then the R^2_A value will actually decline.[24] It is observed that by the addition of MR to the model (Eq. 1), R^2_A increased which also supports the bivariant dependence of biological activity. Hence, multiple regression has been sought.

The regression technique was applied through the origin using these explainable parameters. The resulted modeled equations explain the biological activity as a function of MR and $Q\log P$. Hence, on carrying out regression with MR and $Q\log P$, the correlation equation was obtained as:

$$A = 2.207 \times 10^{-2}(0.003) \times \mathrm{MR} - 0.314(0.105) \times Q\log P, \quad (1)$$

$$N = 50;\ R = 0.938;\ \%\mathrm{EV} = 88.0;\ \mathrm{SEE} = 0.787;\ F = 176.490,$$

Table 2. Correlation matrix of the ABXa analogs

	Activity	$Q\log P$	MR	$Q\log P^2$	MR^2
Activity Pearson Correlation	1.000	−0.385	−0.059	−0.359	−0.061
Sig.(2-tailed)	—	0.006	0.683	0.010	0.675
$Q\log P$ Pearson Correlation		1.000	0.273	0.984	0.276
Sig.(2-tailed)		—	0.055	0.000	0.053
MR Pearson Correlation			1.000	0.264	0.999
Sig.(2-tailed)			—	0.064	0.000
$Q\log P^2$ Pearson Correlation				1.000	0.267
Sig.(2-tailed)				—	0.061
MR^2 Pearson Correlation					1.000
Sig.(2-tailed)					—

$N = 50$.

Table 3. Correlation matrix of the ABXa analogs

	Activity	$Q\log P$	MR	$Q\log P^2$	MR^2
Activity Pearson Correlation	1.000	−0.518	0.152	−0.515	0.151
Sig.(2-tailed)	—	0.001	0.370	0.001	0.373
$Q\log P$ Pearson Correlation		1.000	0.188	0.985	0.187
Sig.(2-tailed)		—	0.264	0.000	0.267
MR Pearson Correlation			1.000	0.169	0.999
Sig.(2-tailed)			—	0.316	0.000
$Q\log P^2$ Pearson Correlation				1.000	0.168
Sig.(2-tailed)				—	0.321
MR^2 Pearson Correlation					1.000
Sig.(2-tailed)					—

$N = 37$.

Table 4. Observed activity and predicted activity values of ABXa analogs (model Eq. 14)

Compound	Observed activity	Predicted value	Residual value
ABXa1	2.0000	1.9037	0.0963
ABXa2	2.1550	1.8439	0.3111
ABXa3	2.3979	1.7973	0.6006
ABXa4	1.9206	1.7416	0.1790
ABXa5	1.4564	1.6856	−0.2292
ABXa7	1.2765	2.1515	−0.8750
ABXa10	2.1675	2.1600	0.0075
ABXa11	2.1612	2.1137	0.0475
ABXa12	2.9586	2.5658	0.3928
ABXa13	2.6990	3.1094	−0.4104
ABXa14	1.3979	2.3793	−0.9814
ABXa15	3.0458	2.2667	0.7791
ABXa19	2.2366	1.8563	0.3803
ABXa20	1.7959	1.7554	0.0405
ABXa21	1.8239	1.6956	0.1283
ABXa23	1.8239	2.1752	−0.3513
ABXa28	1.7696	2.2283	−0.4587
ABXa29	1.8239	2.1824	−0.3585
ABXa30	2.3010	2.6346	−0.3336
ABXa31	2.4437	2.2966	0.1471
ABXa32	3.0458	2.2496	0.7962
ABXa33	1.9586	2.1970	−0.2384
ABXa34	2.8539	2.8398	0.0141
ABXa35	3.0000	2.7929	0.2071
ABXa36	3.1549	2.7330	0.4219
ABXa37	3.0969	2.6784	0.4185
ABXa38	2.6990	2.7477	−0.0487
ABXa39	3.5229	2.7023	0.8206
ABXa40	2.8239	2.8031	0.0208
ABXa41	2.4202	2.7505	−0.3303
ABXa42	2.2007	2.6916	−0.4909
ABXa43	2.4559	2.7484	−0.2925
ABXa44	2.8861	2.7022	0.1839
ABXa45	2.8239	2.7350	0.0889
ABXa46	2.0000	2.2646	−0.2646
ABXa49	1.4559	2.6095	−1.1536
ABXa50	3.6990	2.7897	0.9093

where N is the number of data points, R is the regression constant, %EV is the percentage of explained variance, SEE is the standard error estimation, and F is the F ratio.

Eq. 1 shows that the value of %EV is 88.0 and to improve its value, outliers were sought and eliminated. In addition, the plot of observed activity versus predicted activity was not found to be satisfactory. Hence, the predictive ability of the model is not good.

After the elimination of the outlier ($ABXa_{47}$), a second model was developed.

$$A = 2.229 \times 10^{-2}(0.002) \times \mathrm{MR} - 0.313(0.101) \times Q\log P, \quad (2)$$

$$N = 49;\ R = 0.945;\ \%\mathrm{EV} = 89.3;\ \mathrm{SEE} = 0.753;\ F = 195.266.$$

Eq. 2 is an improved model since it explains the biological activity to the extent of 89.3%. In this way, the predictive molecular descriptors MR and $Q\log P$ were taken as variables and different regression models (Table 5) were generated in a phased manner after eliminating the outliers ($ABXa_{17,18,26,24,8,27,9,22,16,48,25,6}$). Overall, there is an increase in R (0.938–0.981) and %EV (88.0–96.2) values, and a decrease in SEE (0.787–0.491) and the F value increases from 176.490 to 441.647. These trends support the statistic validity of Eq. 14 (Table 5). In an attempt to investigate the predictive potential of proposed models, the cross-validation parameters (q^2_{cv} and PRESS) were calculated and used. The predictive power of the equations was confirmed by leave-one-out (LOO) cross-validation method[25] where, compounds are deleted one after another and prediction of the activity of the deleted compound is made based on the QSAR model. Cross-validation evaluates the validity of a model by how well it predicts the data rather than how well it fits the data. The cross-validation parameter, q^2_{cv}, is mentioned in the respective equation (Table 5).

$$q^2_{cv} = \frac{(\mathrm{SD} - \mathrm{PRESS})}{\mathrm{SD}},$$

where the PRESS (predictive residual sum of squares) and SD (standard deviation) values are obtained as

$$\mathrm{PRESS} = \sum(\mathrm{property}_{\mathrm{observed}} - \mathrm{property}_{\mathrm{predicted}})^2,$$

$$\mathrm{SD} = \sum(\mathrm{property}_{\mathrm{observed}} - \mathrm{property}_{\mathrm{mean}})^2.$$

Eq. 14 gives a good q^2_{cv} value. which should be always smaller than %EV. A model is considered to be significant[17] when $q^2_{cv} > 0.3$.

Another cross-validation parameter, PRESS which is the sum of the squared differences between the actual and that predicted when the compound is omitted from

Table 5. Modeled equations for ABXa analogs

Eq. No.	Equations	N	R	%EV	SEE	F
1	$A = 2.207 \times 10^{-2}(0.003)\,\mathrm{MR} - 0.314(0.105)\,Q\log P$ $q^2_{cv} = 0.1234$; PRESS = 29.7356; $Q = 1.1918$	50	0.938	0.880	0.787	176.490
2	$A = 2.229 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.313(0.101)\,Q\log P$ $q^2_{cv} = 0.1272$; PRESS = 26.6765; $Q = 1.2549$	49	0.945	0.893	0.753	195.266
3	$A = 2.310 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.359(0.099)\,Q\log P$ $q^2_{cv} = 0.1905$; PRESS = 23.9342; $Q = 1.3162$	48	0.949	0.900	0.721	206.430
4	$A = 2.411 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.414(0.100)\,Q\log P$ $q^2_{cv} = 0.2468$; PRESS = 22.0358; $Q = 1.3605$	47	0.951	0.905	0.699	214.169
5	$A = 2.374 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.389(0.099)\,Q\log P$ $q^2_{cv} = 0.2340$; PRESS = 20.7948; $Q = 1.3886$	46	0.954	0.910	0.687	222.790
6	$\mathrm{A} = 2.412 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.396(0.096)\,Q\log P$ $q^2_{cv} = 0.2645$; PRESS = 19.2311; $Q = 1.4326$	45	0.957	0.916	0.668	235.778
7	$A = 2.418 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.391(0.094)\,Q\log P$ $q^2_{cv} = 0.2659$; PRESS = 17.8812; $Q = 1.4723$	44	0.960	0.922	0.652	248.506
8	$A = 2.422 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.384(0.092)\,Q\log P$ $q^2_{cv} = 0.2701$; PRESS = 16.5066; $Q = 1.5189$	43	0.963	0.928	0.634	263.589
9	$A = 2.387 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.359(0.090)\,Q\log P$ $q^2_{cv} = 0.2577$; PRESS = 15.2216; $Q = 1.5681$	42	0.966	0.933	0.616	279.811
10	$A = 2.371 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.342(0.088)\,Q\log P$ $q^2_{cv} = 0.2562$; PRESS = 13.8485; $Q = 1.6285$	41	0.969	0.939	0.595	300.745
11	$A = 2.463 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.375(0.085)\,Q\log P$ $q^2_{cv} = 0.3028$; PRESS = 12.4014; $Q = 1.7022$	40	0.972	0.945	0.571	326.452
12	$A = 2.574 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.415(0.083)\,Q\log P$ $q^2_{cv} = 0.3698$; PRESS = 10.8337; $Q = 1.8022$	39	0.975	0.951	0.541	361.645
13	$A = 2.487 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.365(0.083)\,Q\log P$ $q^2_{cv} = 0.3517$; PRESS = 9.6585; $Q = 1.8880$	38	0.978	0.957	0.518	396.137
14	$A = 2.495 \times 10^{-2}(0.002)\,\mathrm{MR} - 0.359(0.079)\,Q\log P$ $q^2_{cv} = 0.3650$; PRESS = 8.4286; $Q = 1.9979$	37	0.981	0.962	0.491	441.647

N, number of data points; R, regression constant; %EV, percentage of explained variance; SEE, standard error estimation; F, F ratio; q^2_{cv}, cross-validation, PRESS, predictive residual sum of squares; Q, quality factor.

the fitting process, also supports the predictive ability of Eq. 14. Its value decreases from Eq. 1 to Eq. 14 (29.7356–8.4286).

The quality factor,[26] Q, is defined as the ratio of regression constant (R) to the standard error estimation (SEE), that is, $Q = R/\text{SEE}$. This indicates that the higher the value of R, and the lower the value of SEE, the higher is the magnitude of Q and the better will be the correlation. In present case, Q increases from 1.1918 to 1.9979 (Table 5).

The predictive ability of the modeled Eq. 14 is reflected in the low residual values (Table 4). The excellent agreement between observed activity versus predicted activity is shown in Figure 2. The linear relationship between activity and $Q\log P$ is shown in Figure 3. It indicates that as $Q\log P$ increases, the activity decreases, which is also evident from the data (Table 1). As the hydrophobic nature of substituent (R) increases, the activity decreases. So, the compound with low lipophilicity is expected to exhibit higher inhibitory activity. The compound $ABXa_{50}$, with the lowest lipophilicity, showed strong antithrombotic activity (Table 1). A similar observation[18] was made in the vivo study on rabbits.

The bulkiness of the substituent also affects the activity. Its contribution is expected to be marginal since the coefficient value is found to be low (2.495×10^{-2}). The linear dependence of activity on MR is evident from Figure 4.

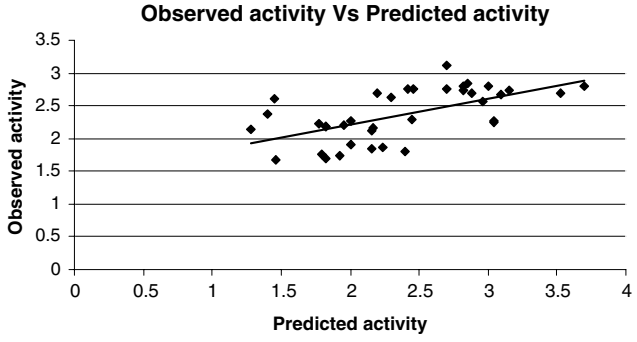


Figure 2. Plot of observed versus predicted activity.

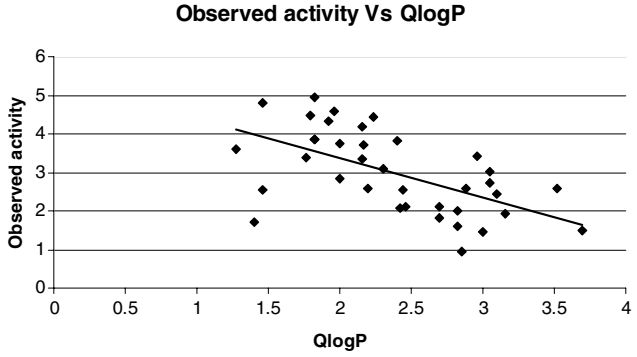


Figure 3. Plot of observed activity versus $Q\log P$.

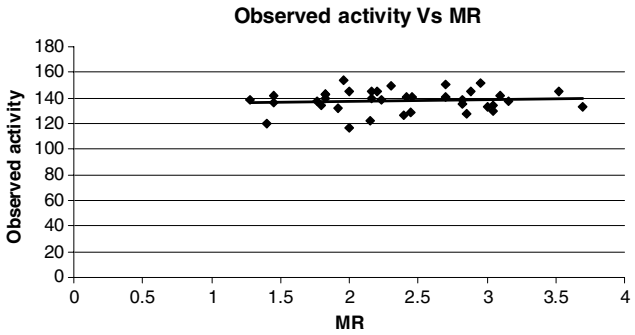


Figure 4. Plot of observed activity versus MR.

Acknowledgment

One of the authors (N.R.) is thankful to The Head, Department of Chemistry, Nizam College, Osmania University, for providing the facilities for the work.

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