

Modelling anticonvulsant activity of some quinazoline derivatives

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Manuscript received online 21 November 2022, accepted on 10 January 2023

Abstract : In this work, an attempt has been made to model the anticonvulsant activity of 22 quinazoline derivatives. The activity has been modelled using some 2d parameters calculated by Dragon software. The best four-parametric model has been obtained which was used for the estimation of the activity values. They were in good agreement with observed values showing that proposed model is best for modelling the activity of present set of compounds. The R² value for the best model comes out to be 0.8628 after deleting two outliers. The model was tested using Leave one out method. The R² CV value for the model comes out to be 0.9206 and the proposed model is free from any defect.

(Keywords : QSAR study, Anticonvulsant activity, Topological parameters, Quinazoline derivatives, Correlation)

Introduction

Epilepsy is a ubiquitous disease which has taken grip of almost 80% of the people in developing countries. It is characterized by chronic and recurrent seizures caused by brief and excessive electrical discharges effecting brain cells^{1,2}. The World Health Organization (WHO) mentioned in its report that most of the people suffering from epilepsy do not receive adequate medication. Mariia Nesterkina et al³ have presented a Quantitative structure–activity relationship (QSAR) study on 36 terpene derivatives with anticonvulsant activity in timed pentylenetetrazole (PTZ) infusion test. They have proposed QSAR models for anticonvulsant activity of hydrazones and esters of some monocyclic/bicyclic terpenoids. These models were developed using simplex representation of

molecular structure (SiRMS; informational field [IF]) approach based on the SiRMS and the IF of molecule. Four 2D partial least squares QSAR consensus models were developed with the coefficient of determination for test sets R² test>0.62 The QSAR models proposed by them might be utilized to predict anticonvulsant effect among terpene derivatives for their oral administration against onset seizures.

In fact for the last forty years the Quantitative structure–activity relationship (QSAR) analysis is widely applied for virtual screening of potential bioactive com-pounds followed by their structure optimization. This method is widely used and acceptable because the methods allow discovering correlation between numerical physicochemical property or molecular feature of compounds and their biological or pharmacological activity which helps in further design of new compounds⁴. The QSAR study published by Nesterkina et al⁵ is a logical continuation of their research devoted to the QSAR analysis for a number of terpene derivatives.

In tune with many theoretical chemists Agrawal and coworkers⁶⁻¹⁰ also proposed many QSAR models for estimating biological activities of various compounds. They have successfully used topological descriptors for modeling the biological activities of drug molecules including CA inhibitors.

The carbonic anhydrase inhibition (CA; EC 4.2.1.1) has demonstrated interesting

pharmacologic applications such as anti-convulsant, anti-glaucoma and anti-cancer agents^{11,12}. These enzymes have shown a potential target for designing anti-convulsant drugs with a novel mechanism of action. The enzymes play an important role in the anion exchange processes. CA isozymes have been described to date in mammals and among them as catalysts for carbon dioxide hydration is CA II. This will allow the maintenance of pH homeostasis in the human body¹³.

It was reported that a series of quinazoline derivatives were designed and synthesized as potential CA inhibitor. Moreover, a literature survey reveals that the chemistry of quinazolines and their derivatives has received considerable attention owing to their synthetic and effective anticonvulsant importance¹⁴. Methaqualone and mecloqualone, as quinazoline analogues, approved as anticonvulsant drugs and the 6-chloro derivative was found to possess remarkable anticonvulsant potency against electroshock-induced convulsions (1.5 times than phenytoin sodium) and against pentylenetetrazol (PTZ)-induced seizures (10 times than troxidone). Over the years, medicinal chemists have modified and substituted different chemical moieties at position 3 of 4(3H)-quinazoline to yield structural analogues with potent anticonvulsant activity.

The recent reported quinazoline analogues (possess significant anti-convulsant activities (ED₅₀ = 73.1 and 11.79 mg/kg) and showed a 100% protection against PTZ induced clonic convulsion¹⁵.

Based on the aforementioned considerations, bearing in mind the inherited anticonvulsant potency of quinazoline nuclei together with the similarities between methaqualone, mecloqualone, the reported anti-convulsants of synthesized derivatives, the anticonvulsant activity of the reported synthesized compounds have been modelled using

some topological parameters. These parameters have been found to be very effective in modelling the activity and the statistical analysis suggested excellent multi-parametric model which are discussed below.

Presentation of data:

The used compounds, their structural details and anticonvulsant activity in the form of scPTZ as reported by Abuelizz et al.¹⁵, are presented in Table-1. The molecular structures were drawn using ACD Labs Chem Sketch [16].software. The mol files have been made and used for calculation of topological indices using Dragon software¹⁷. In Table 2 all the topological parameters calculated are reported. Table-3 reports the correlation matrix obtained using NCSS software¹⁸ showing the intercorrelation among the parameters and also the activity.

The activity in terms of scPTZ of present set of compounds are as below:

8 = 13 = 18 > 15 = 16 > 21 > 3 = 6 = 19 = 22 > 1 = 10 = 11 > 2 = 4 = 9 = 12 = 20 > 14 > 5 > 17

Therefore, it is not easy to establish any one is to one structure-activity relationship on the basis of molecular structures. Hence the data was subjected to regression analysis. A correlation matrix has been derived using the dependent and independent parameters which is reported in Table 3.

A close look of Table 3 reveals that none of the parameters are correlated to activity hence no one-parametric correlation is possible for modeling the activity of present set of compounds. Hence the multi-parametric models were tried. The results obtained by stepwise regression analysis using NCSS software¹⁸ are reported in Table 4.

Results and Discussion:

The step-wise regression analysis gave statistically significant regression equations which are given below:

One-parametric

The only one-parametric correlation is reported below. It has very poor correlation with used parameter MATS4e with activity.

scPTZ= $58.6316 + 192.1668 (\pm 90.5493)$
 MATS4e $N=22$, SE= 24.528, $R^2=0.1838$, Adj $R^2=0.143$, F-ratio=4.504, Q-value=0.0174

Here N is total no. of compounds used, standard error of estimation, R^2 is the square of the correlation coefficient, Adj R^2 is adjusted R^2 , F is Fisheros ratio, Q is Pogliani's constant ($Q=R/SE$)^{19,20}

Two- parametric model

To find out a better model combinations of two parameters were tried. One with Eig05_AEA(dm) and Eig09_AEA(dm) has been found to give best correlation with $R^2 = 0.5872$. The Q value for this model comes out to be 0.0428. The model is as under:

scPTZ= $-322.9194 + 208.8982 (\pm 40.1934)$
 Eig05_AEA(dm) $-123.7254 (\pm 24.5766)$
 Eig09_AEA(dm)
 $N=22$, SE= 17.892, $R^2 = 0.5874$, Adj $R^2 = 0.544$, F-ratio= 13.526, Q-value= 0.0428

Three-parametric model

When Eig12_AEA(bo), Eig05_AEA(dm) and SpMax3_Bh(i) were taken together a three-parametric model was obtained with a very significant increase in R^2 value. The vlues changed from 0.5874 to 0.6942. Also the -value increased dignificantly. The model is given below:

scPTZ= $-1038.0515 -124.0120 (\pm 20.0654)$
 Eig12_AEA(bo)+ $228.4827 (\pm 35.9590)$
 Eig05_AEA(dm)+ $179.3931 (\pm 47.8046)$
 SpMax3_Bh(i)
 $N=22$, SE= 15.826, $R^2 = 0.6942$, Adj $R^2 = 0.6432$, F-ratio= 13.62, Q-value= 0.0526

Four-parametric model

To get betterbmodel several four-parametric correlations were tried. One with) Eig12_AEA(bo), Eig05_AEA(dm), VE1_D/Dt, SpPosLog_Dz(p) gave excellent results. The R^2 for this model is 0.8628 which is better than

earlier value for three-parametric correlation obtained earlier. Other parameters have significant changes. The model is as given below:

scPTZ= $525.0433 -105.1943 (\pm 13.9781)$
 Eig12_AEA(bo) + $171.1710 (\pm 25.5353)$
 Eig05_AEA(dm) $-282.2323 (\pm 40.6121)$
 VE1_D/Dt+ $75.5628 (\pm 12.8521)$
 SpPosLog_Dz(p)
 $N=22$, SE= 10.908, $R^2 = 0.8628$, Adj $R^2 = 0.8305$, F-ratio= 26.725, Q-value= 0.0852

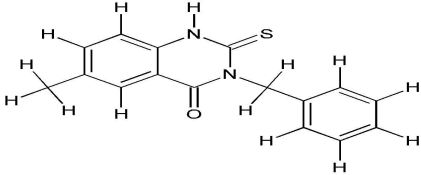
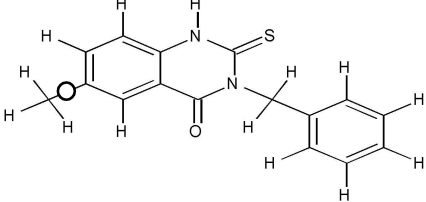
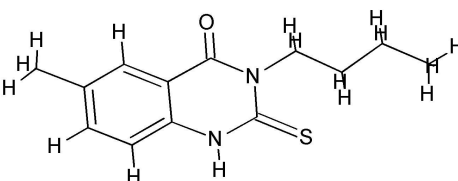
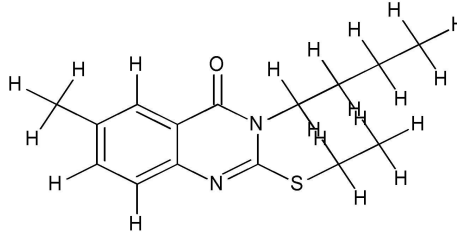
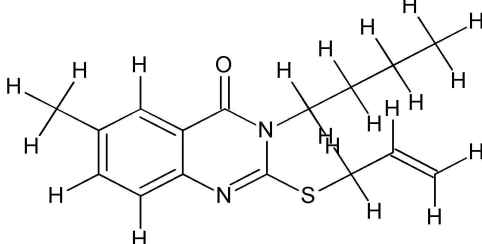
It has been found that two compounds are behaving as outliers, hence they were .removed from the data. With 20 compounds the best four-parametric model was obtained. The R^2 value for this model comes out to be 0.9264 which is much higher than the previous value 0.8628. The model is as follows:

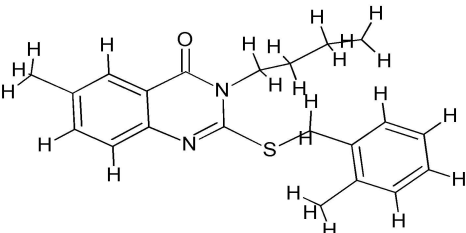
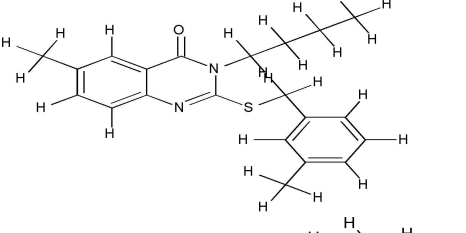
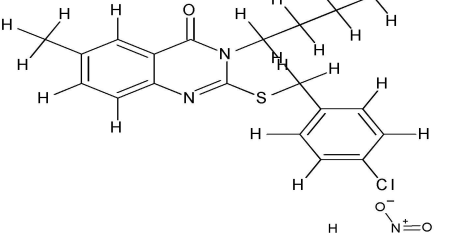
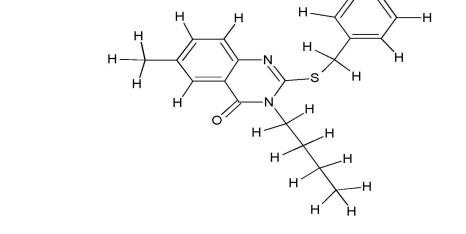
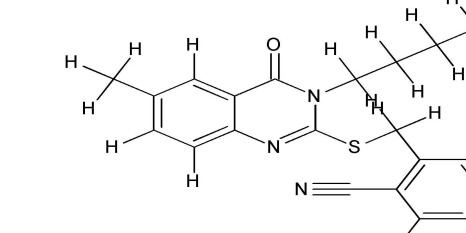
scPTZ= $516.4444 -101.3801 (\pm 10.0771)$
 Eig12_AEA(bo)+ $162.3511 (\pm 18.3543)$
 Eig05_AEA(dm) $-275.9174 (\pm 29.5273)$
 VE1_D/Dt+ $75.2407 (\pm 9.4010)$
 SpPosLog_Dz(p)
 $N=20$, SE= 7.791, $R^2 = 0.9264$, Adj $R^2 = 0.9068$, F-ratio= 47.229, Q-value= 0.1235

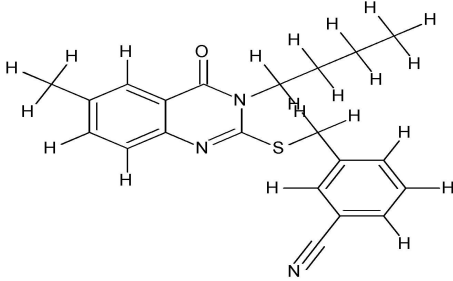
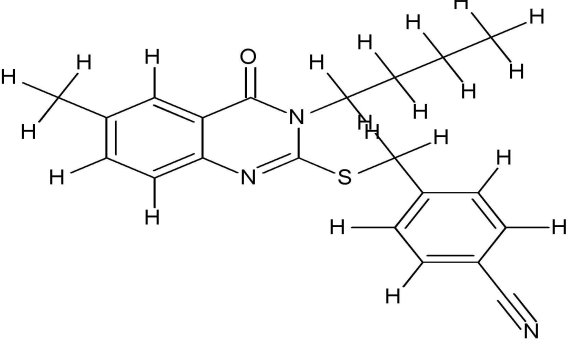
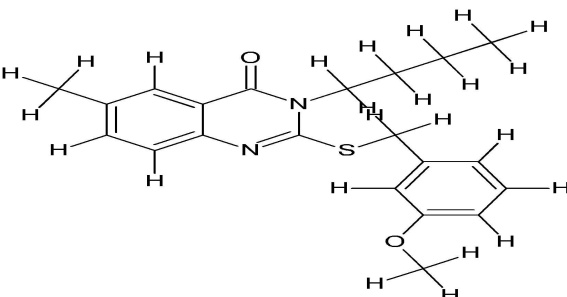
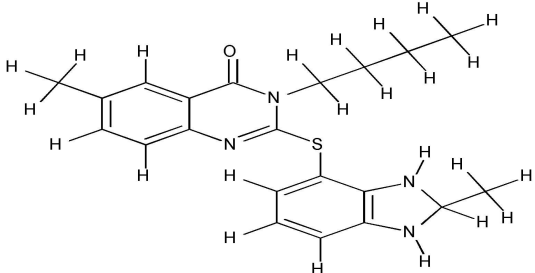
The best model was used for estimating the anticonvulsant activities (scPTZ) of present set of compounds. Such values are given in Table 5. The estimated values are close to observed values confirming that the proposed model is excellent. The predictive power of the model was calculated by plotting a graph between observed and estimated scPTZ values. The graph is given in Fig. 2. The predited power of the model comes out to be 0.9264.

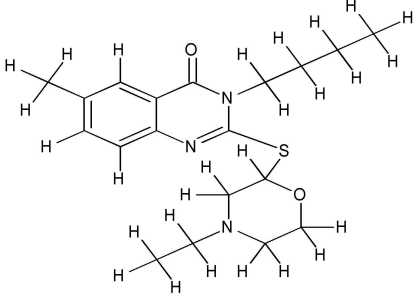
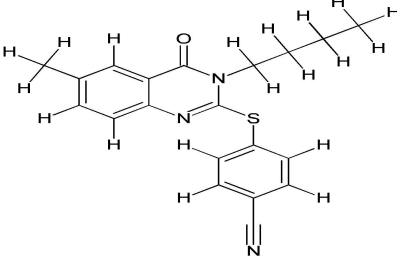
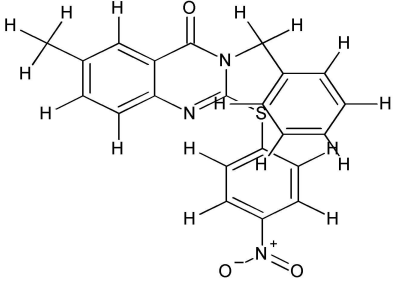
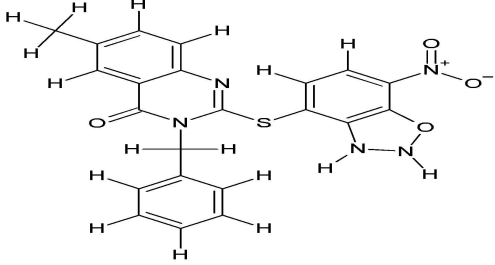
The best four-parameteric model has been tested using cross validated method²¹. The R^2_{CV} for the best model comes out to be 0.9206. All other cross validated parameters , PSE, SPRESS, PRESS/ SSV also confirm that the model is best among all proposed models. The model proposed is free from the defect of colinearity which is confirmed by the VIF (Fig. 3) and Rigde plot (Fig. 4).

Table 1:
The structural details of the compounds alongwith anticonvulsant activity of
compounds used in the present study.

Comp.No.	Structure of compounds	Acitivity (scPTZ)
1		50
2		33
3		67
4		33
5		20

Comp.No.	Structure of compounds	Activity (scPTZ)
6		67
7		67
8		100
9		33
10		50

Comp.No.	Structure of compounds	Acitivity (scPTZ)
11		50
12		33
13		100
14		25

Comp.No.	Structure of compounds	Acitivity (scPTZ)
15		83
16		83
17		17
18		100

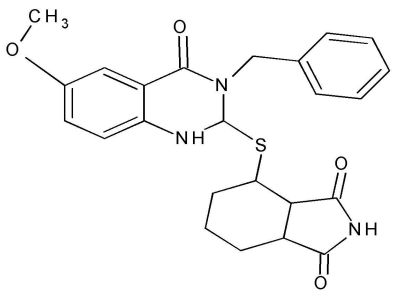
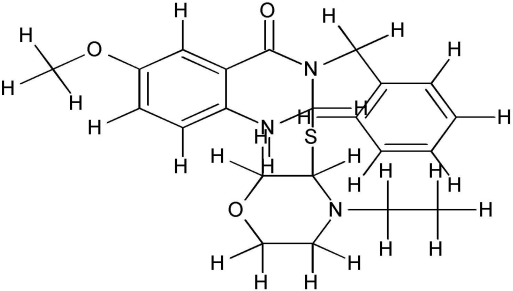
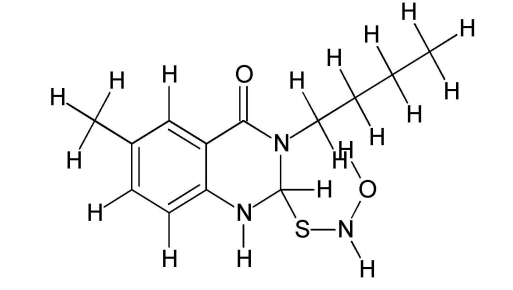
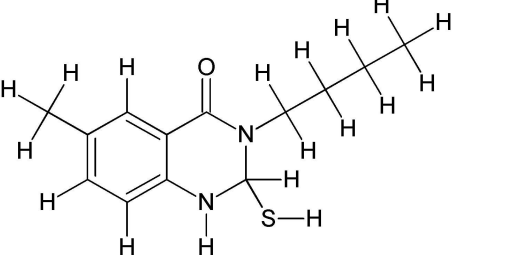
Comp.No.	Structure of compounds	Acitivity (scPTZ)
19		67
20		33
21		75
22		67

Table -2
The parameters calculated for the compounds used in the present study.

S.N.	Eig12_AEA(bo)	Eig05_AEA(dm)	Eig09_AEA(dm)	VE1 D/Dt	SpPosLog Dz(p)	MATS4e	SpMax3 Bh(i)
1	0.701	2.296	1	3.83	3.836	0.007	3.58
2	0.934	2.477	1.145	4.046	4.196	-0.071	3.557
3	0.05	2.016	0.259	3.644	3.094	0.029	3.532
4	0.685	2.306	0.887	3.839	3.577	-0.007	3.579
5	0.687	2.308	1.074	3.897	3.839	-0.005	3.626
6	1.356	2.644	1.441	4.113	5.177	0.014	3.755
7	1.316	2.607	1.36	4.124	5.186	0.033	3.755
8	1.356	2.78	1.36	4.097	5.193	-0.059	3.755
9	1.854	2.781	1.756	4.285	5.855	-0.116	3.756
10	1.856	2.783	1.542	4.131	5.451	-0.028	3.755
11	1.836	2.782	1.818	4.164	5.469	-0.036	3.755
12	1.859	2.781	1.851	4.191	5.488	-0.042	3.755
13	1.583	2.776	1.367	4.164	5.555	-0.028	3.755
14	1.806	2.78	1.557	4.286	5.741	0.031	3.755
15	1.417	2.713	1.376	4.072	5.333	0.138	3.753
16	1.529	2.781	1.389	4.079	5.154	-0.01	3.754
17	2.5	2.829	1.812	4.286	6.346	-0.125	3.914
18	2.5	3.25	2.295	4.469	7.229	0.067	3.914
19	2.467	3.398	2.487	4.688	7.302	-0.053	3.523
20	1.878	2.737	1.8	4.474	6.508	-0.001	3.86
21	0.592	2.306	0.822	3.839	3.687	0.054	3.552
22	0.021	2.035	0.263	3.644	3.101	0.016	3.544

Table - 3
Correlation matrix

	scPTZ (act.)	Eig12_AEA (bo)	Eig05_AEA (dm)	Eig09_AEA (dm)	VE1 D/Dt	SpPosLog_ Dz(p)	MATS4e	SpMax3_ Bh(i)
scPTZ(act.)	1							
Eig12_AEA(bo)	-0.0308	1						
Eig05_AEA(dm)	0.1926	0.9443	1					
Eig09_AEA(dm)	-0.0292	0.9615	0.9576	1				
VE1 D/Dt	-0.0211	0.9332	0.9397	0.9565	1			
SpPosLog_Dz(p)	0.0857	0.9689	0.9575	0.9535	0.9726	1		
MATS4e	0.4287	-0.3145	-0.2063	-0.2742	-0.2655	-0.2085	1	
SpMax3_Bh(i)	0.0364	0.7273	0.5737	0.6071	0.57452	0.6989	-0.088	1

Table - 4
Quality of correlation for various models obtained

Model No.	Parameter	Ai, i=1,2,3,....	Intercept	Se	AdjR ²	R ²	F-Ratio	Q-Value
1	MATS4e	A1=192.1668 (±90.5493)	58.6316	24.528	0.143	0.1838	4.504	0.0175
2	Eig05_AEA(dm) Eig09_AEA(dm)	A1=208.8982 (40.1934) A2=-123.7254 (±24.5766)	-322.919	17.892	0.544	0.5874	13.526	0.0428
3	Eig12_AEA(bo) Eig05_AEA(dm)	A1=-72.1625 (±18.9073) A2=160.8732 (±40.4385)	-267.408	20.565	0.3976	0.455	7.93	0.0328
4	Eig05_AEA(dm) VE1 D/Dt	A1=142.6757 (± 41.2900) A2=-176.5340 (±53.7025)	404.8223	21.824	0.3216	0.3862	5.977	0.0285
5	Eig12_AEA(bo) Eig05_AEA(dm) SpMax3 Bh(i)	A1=-124.0120 (±20.0654) A2=228.4827 (±35.9590) A3=179.3931 (±47.8046)	-1038.05	15.826	0.6432	0.6942	13.62	0.0526
6	Eig05_AEA(dm) Eig09_AEA(dm) MATS4e	A1=192.6118 (±37.6967) A2=-110.1609 (±23.4528) A3=137.0848 (± 64.4174)	-297.568	16.431	0.6154	0.6704	12.201	0.0498
7	Eig12_AEA(bo) Eig05_AEA(dm) Eig09_AEA(dm)	A1=-34.8784 (±19.5415) A2=230.0731 (±39.8697) A3=-92.2664 (±29.1952)	-373.945	16.944	0.591	0.6495	11.116	0.0475
8	Eig05_AEA(dm) Eig09_AEA(dm) VE1 D/Dt	A1=225.0696 (±40.8861) A2=-100.1773 (±29.2985) A3=-73.4249 (± 52.4872)	-96.9107	17.458	0.5659	0.6279	10.124	0.0454
9	Eig12_AEA(bo) Eig05_AEA(dm) VE1 D/Dt SpPosLog_Dz(p)	A1=-105.1943 (±13.9781) A2=171.1710 (±25.5353) A3=-282.2323 (±40.6121) A4=75.5628 (±12.8521)	525.0433	10.908	0.8305	0.8628	26.725	0.0851
10	Eig12_AEA(bo) Eig05_AEA(dm) Eig09_AEA(dm) SpMax3 Bh(i)	A1=-86.3752 (±21.7708) A2=266.1305 (±33.4732) A3=-67.9172 (±24.3244) A4=144.1295 (±42.6432)	-964.987	13.484	0.741	0.7903	16.021	0.0659
11	Eig12_AEA(bo) Eig05_AEA(dm) VE1 D/Dt SpMax3 Bh(i)	A1=-104.7368 (±20.5093) A2=255.4234 (± 35.3037) A3=-84.8470 (±40.1269) A4=157.3161 (±44.9984)	-705.984	14.4906	0.7009	0.7579	13.303	0.0601
12	Eig05_AEA(dm) Eig09_AEA(dm) VE1 D/Dt MATS4e	A1=207.9165 (± 38.4884) A2=-89.5890 (±27.4154) A3=-66.0898 (±48.3832) A4=130.7819 (± 63.0907)	-95.3032	16.05007	0.6331	0.703	10.058	0.0522
13	Eig12_AEA(bo) Eig05_AEA(dm) Eig09_AEA(dm) MATS4e	A1=-25.8529 (±19.2616) A2=211.1351 (±39.3817) A3=-89.1977 (±27.7583) A4=113.2835 (± 65.4764)	-339.791	16.077	0.6318	0.7019	10.009	0.0521

		After deleting compound number .13, 21						
14	Eig12_AEA(bo) Eig05_AEA(dm) VE1_D/Dt SpPosLog_Dz(p)	A1=-101.3801(± 10.0771) A2=162.3511 (±18.3543) A3=-275.9174 (±29.5273) A4=75.2407 (±9.4010)	516.4444	7.791	0.9068	0.9264	47.229	0.1235

Table -5
The predicted scPCZ values using model 13 (Table 4)

Compd No .	Observed	Predicted	Difference
1	50	53.22	-3.22
2	33	25.932	7.068
3	67	70.201	-3.201
4	33	34.504	-1.504
5	20	38.064	-18.064
6	67	65.343	1.657
7	67	60.793	6.207
8	100	94.347	5.653
9	33	39.094	-6.094
10	50	52.163	-2.163
11	50	46.142	3.858
12	33	37.367	-4.367
13	100	78.227	21.773
14	25	35.076	-10.076
15	83	94.096	-11.096
16	83	78.453	4.547
17	17	16.174	0.826
18	100	103.311	-3.311
19	67	75.823	-8.823
20	33	25.039	7.961
21	75	52.599	22.401
22	67	77.033	-10.033

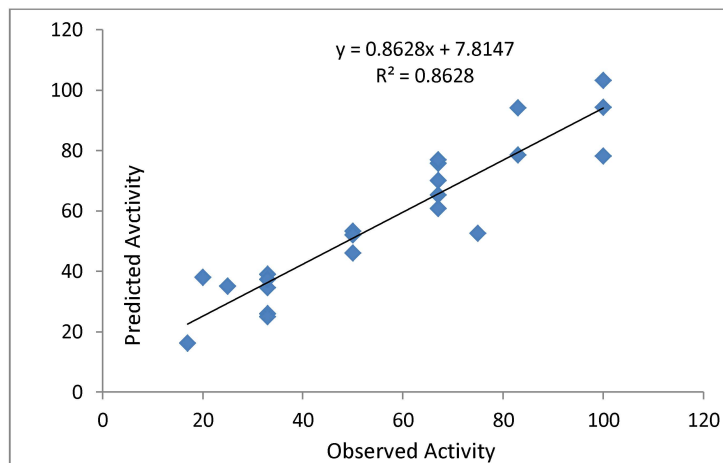


Fig. 1. A plot between observed and predicted activity using model 13 (Table 4)

Table 6.

Predicted activity values using model 14 (table 4) after deleting compound no. 13, 14.

Compd No.	Observed Activity	Predicted Activity	Residual
1	50	49.995	0.005
2	33	23.247	9.753
3	67	66.027	0.973
4	33	31.27	1.73
5	20	35.101	-15.101
6	67	62.902	4.098
7	67	58.592	8.408
8	100	90.6	9.4
9	33	38.212	-5.212
10	50	50.428	-0.428
11	50	44.542	5.458
12	33	36.028	-3.028
13	25	34.063	-9.063
14	83	90.97	-7.97
15	83	75.256	7.744
16	17	17.181	-0.181
17	100	101.475	-1.475
18	67	73.915	-6.915
19	33	25.619	7.381
20	67	72.578	-5.578

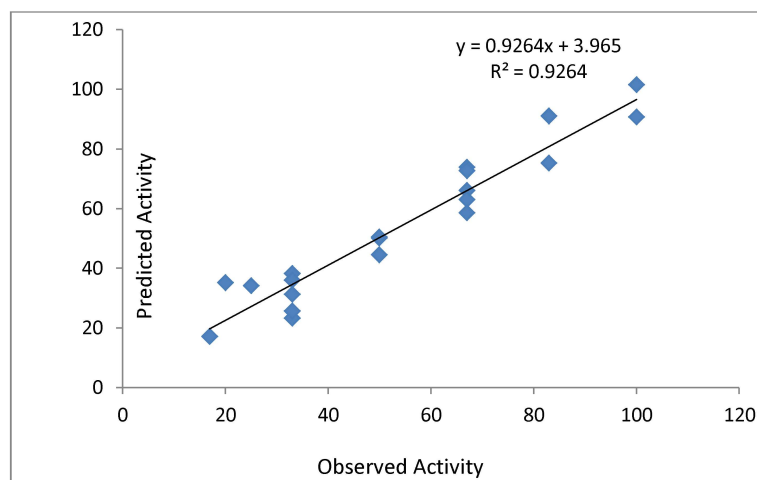


Fig 2. Plot between observed predicted activity using model 14 (Table 4)

Table 6.
The Cross validated parameters for the obtained models.

MODEL NO	NO OF DESCRIPTOR	N	PRESS	SSY	PRESS/SSY	R ² CV	PSE	SPRESS
1	MATS4e	22	12033.16	2709.797	4.4406	-3.4406	23.387	24.528
2	Eig05_AEA(dm),Eig09_AEA(dm)	22	6082.664	8660.291	0.7023	0.2977	16.627	17.892
3	Eig12_AEA(bo),Eig05_AEA(dm),SpMax3_Bh(i)	22	4508.437	10234.52	0.4405	0.5595	14.315	15.826
4	Eig12_AEA(bo),Eig05_AEA(dm),VE1_D/Dt, SpPosLog_Dz(p)	22	2022.843	12720.11	0.159	0.841	9.588	10.908
5	Eig12_AEA(bo),Eig05_AEA(dm),Eig09_AEA(dm),SpMax3_Bh(i)	22	3090.952	11652	0.2652	0.7348	11.853	13.484
After deleting compound .No.13 ,21								
6	Eig12_AEA(bo),Eig05_AEA(dm),VE1_D/Dt, SpPosLog_Dz(p)	20	910.5041	11467.3	0.0794	0.9206	6.747	7.791

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