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Quantitative Structure Activity Relationship of Riluzole Series as Anticonvulsants

A. GUNAKKUNRU* and S.M. VERMA
Department of Pharmaceutical Sciences, Birla Institute of Technology
Mesra, Ranchi-835 215, India
E-mail: gunakkunru.a@gmail.com

24 Riluzole series, a blocker of excitatory amino acid (glutamic acid) mediated transmission, 2-benzothiazol-amines and 3-substituted 2-imino benzothiazolines have been subjected to quantitative structure activity relationship studies by step wise multiple regression analysis using steric, electronic descriptors. Result of this study has given 12 QSAR models and among all models one has statistically significant result ($r > 0.97$, $F = 133.4899$, $q^2 = 0.97753$). Descriptors used in this study are: polarizability, density, molar refractivity, molar volume, average mass, parachor. Predictive ability of proposed model was assessed on the basis of regression data and cross validation parameters. This validated model brings important structural insight to model better anticonvulsant containing benzothiazole nucleus and more potent than riluzole.

Key Words: QSAR, Riluzole series, Benzothiazoles analogs, Anticonvulsants, Antiglutamate.

INTRODUCTION

There is currently need for improved agents for the treatment of seizure disorders, since available drugs are effective in only 60-80% of epileptic patients[1,2]. Absence seizures are well controlled in most cases but significant therapeutic advancement is required for the treatment of partial-complex (focal) seizures and generalized tonic-clonic (grand mal) epilepsy. In pharmacological experiments show that riluzole possessed anticonvulsant properties in different models including maximal electroshock in mice, convulsion induced by glutamic acid decarboxylase inhibitors in mice and rats, sound-induced convulsions in DBA/2 mice, photo sensitive epilepsy in baboons. However unlike benzodiazepines, barbiturates, valproic acid, riluzole was ineffective against seizures induced by pentylenetetrazole and picrotoxin. Riluzole has been shown to have interesting neuroprotective effects *in vitro*, protecting primary culture of rat cortical neurons against anoxic stress. Furthermore rat motoneurons were protected by riluzole from the excitotoxocity effects of glutamic acid

uptake inhibitors. These studies suggested that riluzole may have neuroprotective effects in whole animal models of cerebral ischemia. Clinical studies have shown that riluzole can slow down the disease progression in amylotropic lateral sclerosis.

Thus, there is hope to find more potent anticonvulsant drug from riluzole series. The present study has concerned with bringing up new QSAR model to develop better anticonvulsant containing benzothiazole nucleus. QSAR study already reported in substituted 2-benzothiazolamine as sodium flux inhibitors series with anticonvulsant property. In the present study concerning with different descriptors and has developed statistically significant results (Table-1) when comparing to already reported QSAR model[1], however for this study compounds are taken from different source and 3-substituted imino benzothiazolines were used with their ED_{50} values (protection against glutamic acid evoked convulsion).

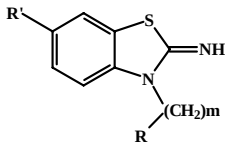
TABLE-1

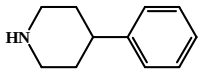
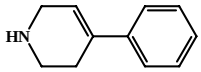
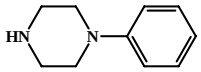
Eq. No.	q^2	PRESS / SSY	S_{PRESS}	Q	SDEP	F
1	-3.179000	4.179002	0.379992	1.156385	0.898283	0.897344
2	0.278779	0.721221	0.273828	2.783585	0.237142	5.199512
3	0.127780	0.872220	0.288732	2.531197	0.250050	4.299375
4	0.646136	0.353864	0.216268	3.973936	0.187293	10.597300
5	0.635111	0.364889	0.218722	3.913436	0.189419	10.277090
6	0.633965	0.366035	0.218973	3.907308	0.189637	10.244920
7	0.894756	0.105244	0.130536	7.286867	0.113047	35.631590
8	0.837438	0.162562	0.158184	5.863123	0.136991	23.068080
9	0.896918	0.103082	0.129315	7.362880	0.111990	36.378850
10	0.901218	0.098782	0.126836	7.521439	0.109843	37.962550
11	0.949280	0.050720	0.093478	10.436260	0.079440	64.077100
12	0.977526	0.022474	0.061180	16.180880	0.051350	133.489900

EXPERIMENTAL

Anticonvulsant ED_{50} value of glutamic acid evoked convulsion values and their corresponding structures are given in Table-2. These values are work of Patrick Jiminet *et al.*[2]. 3-Substituted imino benzothiazolines were taken in present studies. These ED_{50} values are converted into log (ED_{50}) and all the compounds in both training and test set were drawn in chem. Sketch physiochemical properties were calculated by ACD lab freeware release 8.00 version 8.17, only 2D descriptors were calculated from drawing the molecules in chemsketch. The following descriptors were calculated *viz.*, polarizability(pol), average mass (AM), parachor (Pc), molar refractivity (MR), molar volume (MV), surface tension (ST), index of refraction (η), density (D) and indicator parameter (I) (presence of 6-trifluoromethoxy group in benzothiazole)[3].

TABLE-2
6-TRIFLUOROMETHOXY 3-IMINO BENZOTHIAZOLINES



Name	ED_{50} (mg/kg)	(CH_2)n-R			log ED_{50}	
		N	R	R´	Observed	Predicted
1^T	3.0	1	SCH_3	6-OCF_3	0.4771	0.40412
2	2.3	1	SCH_3	6-OCF_3	0.3617	0.33280
3^*	1.0	2	SCH_3	6-OCF_3	0.0000	---
4	2.2	2	SC_2H_5	6-OCF_3	0.3424	0.34280
5	2.4	2	SC_3H_8	6-OCF_3	0.3802	0.35070
6^*	1.1	2	$S(O)CH_3$	6-OCF_3	0.0414	---
7	1.8	2	$S(O)_2CH_3$	6-OCF_3	0.2553	0.34740
8	2.0	2	SH	6-OCF_3	0.3010	0.33700
9	2.3	3	S(O)Me	6-OCF_3	0.3617	0.34910
10	2.0	2		6-OCF_3	0.3010	0.36370
11	3.0	2		6-OCF_3	0.4771	0.42760
12	2.2	2		6-OCF_3	0.3424	0.42600
13	3.5	2		6-OCF_3	0.5441	0.42810
14	12.0	0	0	4-OCF_3	1.0792	1.05200
15	12.0	0	0	5-OCF_3	1.0792	1.05200
16	12.0	0	0	7-OCF_3	1.0792	1.05200
17	2.3	2	NMe_2	6-OCF_3	0.3617	0.32350
18	12.0	2	NMe_2	6-*t*-Bu	1.0792	1.08890
19	12.0	2	S(O)Et	6-*t*-Bu	1.0792	1.11550
20	12.0	2	S(O)Et	6-*n*-Bu	1.0792	1.11460
21^T	2.6	2	$S(O)_2Et$	6-OC_2H_5	0.4150	0.52160
22^T	9.0	3	NMe_2	6-OCF_3	0.9542	0.87950
23^T	7.0	2	$N(Me)CH_2Ph$	6-OCF_3	0.8451	0.80230
24^T	5.0	2	$N(Me)(CH_2)_2Ph$	6-OCF_3	0.6990	0.50890

#compounds taken from reference no.2, Predicted by Equation no.12, the compound no superscripted by T are known as external validation set (not included in developing model), compound no superscripted by *are not included in study.

All the calculated parameters in the ACD labs freeware were considered as independent variables and biological activity [log ED_{50}] was taken as dependent variable. Stepwise regression analysis method was used to develop equations. All the calculated parameters are listed in Table-4.

The statistical parameters were used to find out best regression model among all equation obtained in regression analysis coefficient of correlation (R), F-statistics (F), quality factor (Q) and standard error (Se). In addition to that the best QSAR equation further subjected to internal validation by leave-one-out (LOO) method, external validation by taking 5 compounds in test set, these compounds are,in compound number, superscripted with 'T' and cross validation process[4,5].

TABLE-3
CORRELATION MATRIX OF PARAMETERS USED IN QSAR STUDY

	MV	INR	ST	Avg-mass	Para-chor	Den-sity	Polari-zibili	MR	VI
MV	1								
INR	-0.0009	1							
ST	-0.2415	0.8188	1						
Avgmass	0.8966	0.0907	-0.05006	1					
Parachor	0.9933	0.0982	-0.12886	0.9113	1				
Density	-0.6711	0.2112	0.47532	-0.2774	-0.6288	1			
Polarizibility	0.9923	0.1223	-0.13922	0.9015	0.9980	-0.6395	1		
MR	0.9923	0.1221	-0.13944	0.9015	0.9980	-0.6395	0.9999999	1	
VI	0.3324	-0.2316	-0.15263	0.6357	0.3229	0.2921	0.3007961	0.3009	1

RESULTS AND DISCUSSION

When training set was subjected to stepwise regression multiple linear analysis, in order to develop QSAR model[6-8].

$\log ED_{50} = 12.68 (\eta) + 17.08 (Pol) - 0.044 (ST) - 6.777 (MR) - 17.18$ (1)
R = 0.439417, Q = 1.156385, F = 0.897344, n = 20

$\log ED_{50} = 8.871 (Pol) + 0.036 (ST) - 2.88 (D) - 3.534 (MR) + 4.346$ (2)
R = 0.762222, Q = 2.783585, F = 5.199512, n = 20

$\log ED_{50} = 27.603 (Pol) - 10.855 (MR) - 1.930 (D) - 0.013 (Pc) + 4.733$ (3)
R = 0.730839, Q = 2.531197, F = 4.299375, n = 20

$\log ED_{50} = 8.158 (Pol) + 0.015 (ST) - 0.0131 (AM) - 3.198 (MR) + 1.329$ (4)
R= 0.859434, Q= 3.973936, F= 10.5973, n= 20

$\log ED_{50} = 5.9639 (\eta) + 0.0089 (ST) + 0.012 (MV) - 0.013 (AM) - 7.975$ (5)
R = 0.855956, Q = 3.913436, F = 10.27709, n = 20

$\log ED_{50} = 5.682 (\eta) + 0.0045 (Pc) - 0.012 (AM) - 0.0038 (ST) - 6.914$ (6)
R = 0.855597, Q = 3.907308, F = 10.24492, n = 20

$\log ED_{50} = 0.0014 (Pc) - 0.0061 (ST) - 0.003 (MV) - 0.789 (I) + 1.187$ (7)
R = 0.951198, Q = 7.286867, F = 35.63159, n = 20

$\log ED_{50} = 10.\ 671 (D) + 0.0302 (Pc) - 0.058 (AM) - 0.074 (ST) - 10.372$ (8)
R = 0.927453, Q = 5.863123, F = 23.06808, n = 20

$\log ED_{50} = 3.78 (Pol) + 0.0999 (D) - 1.4956 (MR) - 0.795 (I) + 0.707$ (9)
R = 0.95213, Q = 7.36288, F = 36.37885, n = 20

$\log ED_{50} = 1.563 (\eta) + 0.001 (AM) - 0.01 (ST) - 0.822 (I) - 1.247$ (10)
R = 0.953991, Q = 7.521439, F = 37.96255, n = 20

$\log ED_{50} = 1.062506 (\eta) + 0.001 (AM) - 0.01 (ST) - 0.8148 (I) - 0.44404$ (11)
R = 0.97557, Q = 10.43626, F= 64.0771, n = 18

TABLE-4
DESCRIPTORS USED IN THIS STUDY

Name	log ED_{50}	MV	INR	ST	AVG Mass	Parachor	Density	Polarizability	MR	I
1	0.47712	192.9	1.604	44.4	294.300	498.2	1.520	26.31	66.37	1
2	0.36173	187.5	1.637	56.5	310.310	514.3	1.650	26.69	67.34	1
3	0.00000	209.0	1.594	43.5	308.340	536.8	1.470	28.13	70.98	1
4	0.34242	225.1	1.586	42.6	322.300	575.4	1.430	29.96	75.59	1
5	0.38021	241.1	1.579	42.0	336.399	614.0	1.390	31.79	80.19	1
6	0.04139	203.6	1.624	54.3	324.340	552.9	1.590	28.52	71.94	1
7	0.25527	214.8	1.594	49.0	340.340	568.4	1.580	28.90	72.92	1
8	0.30103	187.9	1.620	44.2	294.300	485.0	1.560	26.19	66.07	1
9	0.36173	219.7	1.613	52.5	338.370	591.5	1.540	30.35	76.55	1
10	0.30103	241.9	1.603	45.5	345.800	628.5	1.420	32.98	83.19	1
11	0.47712	309.8	1.616	45.6	421.480	805.4	1.360	42.93	108.30	1
12	0.34242	309.8	1.616	45.6	419.470	805.4	1.350	42.93	108.30	1
13	0.54407	304.5	1.624	47.8	422.470	800.9	1.380	42.67	107.65	1
14	1.07918	148.9	1.614	49.2	234.200	394.5	1.572	20.59	51.94	0
15	1.07918	148.9	1.614	49.2	234.200	394.5	1.572	20.59	51.94	0
16	1.07918	148.9	1.614	49.2	234.200	394.5	1.572	20.59	51.94	0
17	0.36173	220.5	1.562	39.4	305.320	552.5	1.380	28.36	71.55	1
18	1.07918	250.9	1.582	38.7	277.430	626.1	1.100	33.22	83.82	0
19	1.07918	250.1	1.628	49.9	310.480	665.1	1.240	35.21	88.82	0
20	1.07918	246.5	1.638	53.0	310.480	665.3	1.250	35.15	88.66	0

I is 'indicator parameter' used in this study, which indicates presence of trifluoro methoxy group at 6th position, 1 indicates presence of group and 0 indicates absence of group.

$$\log ED_{50} = 0.5473\ (\eta) + 0.001\ (AM) - 0.002\ (ST) - 0.7739\ (I) + 0.094609 \quad (12)$$

R = 0.9889, Q = 16.1808, F = 133.4899, n = 17

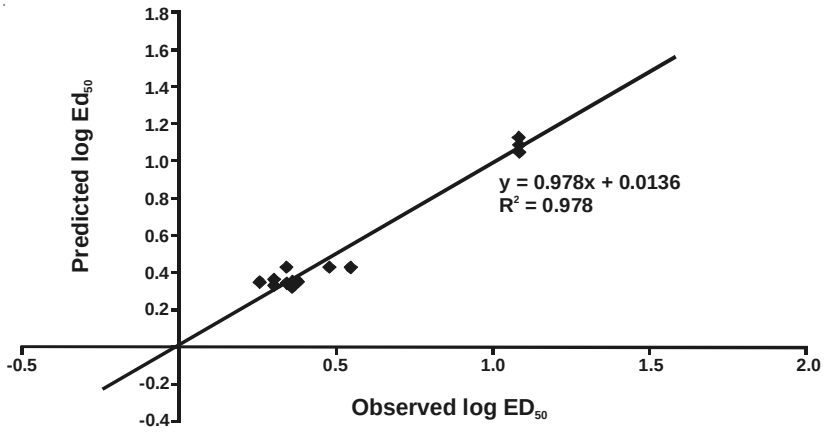


Fig.1 Plot of observed log ED_{50} *vs.* predicted log ED_{50}

All the equations were screened for inter correlation with in descriptors by correlation matrix (Table-3). Internal validation was done by leave-out-one validation method. Among above 12 equations, equation 12th has good statistical significance; equation 1-5 did not comply with cross validation parameter. Hence equation 12 considered to be the best model for predicting the activity. The presence of outliers was tested and 3 outliers were removed equation 11 and 12 are best equation without outliers. Outliers are nothing but values which are higher than two times of standard deviation of predicted value. But simply getting good statistics is not only enough for dealing with biological studies when no proper predictivity is possible. In view of this quality factor Q was used in this study. Use of quality factor Q indicates that all the models under the referred condition have the best predictive power too. In this view we have under gone cross validation methodology for deciding predictive power of the proposed models.

Predicted residual sum of squares (PRESS) appears to be the most important cross-validation parameter. Its value less than SSY (sum of squares of response value) indicate that the model predicts better than chance and can be considered statistically significant. In this model PRESS << SSY indicates its predictive power better than chance. To be a reasonable QSAR model, PRESS/SSY[7-9] should be smaller than 0.4.

The satisfactory values of internal validation cross validation parameters (PRESS/SSY ratio < 0.3), standard deviation of prediction (SPRESS) 0.126, standard deviation of error of predictions (SDEP) 0.1098 are supporting the predictive ability of this model.

Present study shows that index of refraction (η) and average mass (AM) positively correlating with activity and indicator parameter (I) and surface tension (ST) are negatively correlating with activity. From the above model equation can be used to predict the activity for new models.

Conclusion

This study led to the identification of important physiochemical properties in explaining the variation in activity in both training and test set molecules. 3-Substituted imino benzothiazolines with anticonvulsant (antiglutamate) can be modeled excellently by the above equations using index of refraction, surface tension and average mass and indicator parameter. Indicator parameter is important parameter which gives best results, in this case presence of 6-trifluoromethoxy is influencing biological activity. The substitutions at 3-increasing the index of refraction may increase biological activity and presence of 6-trifluoromethoxy increases the activity.

REFERENCES

1. S.J. Hays, M.J. Rice, D.F. Ortwine, G. Johnson, R.D. Schwarz, D.K. Boyd, L.F. Copeland, M.G. Vartanian and P.A. Boxer, *J. Pharm. Sci.*, **83**, 1425 (1994).
2. P. Jiminet, F. Audiau, M. Barreau, J.C. Blanchard, A. Boirau, Y. Bour, M.A. Coleno, A. Doble, G. Doerflinger, C. Do Huu, M.H. Donat, J. Marie, D.P. Ganil, C. Gueremy, E. Honore, B. Just, R. Kerphirique, S. Gontier, P. Hubert, P.M. Laduron, J. Le Blevec, M. Meunier, J.M. Miquet, C. Nemecek, M. Pasquet, O. Piot, J. Pratt, J. Rataud, M. Reibaud, J.M. Stutzmann and S. Mignani, *J. Med. Chem.*, **42**, 2828 (1999).
3. ACD/Chemsketch Reference Manual Version 8.00.
4. D.J. Abraham, Burger's Medicinal Chemistry and Drug Discovery, Wiley Interscience, Vol. 1, p. 49 (2003).
5. A.K. Gupta, L.K.Soni, P. Hanumantharao, S.V. Sambasivarao, M. A. Babu and S.G. Kashedikar, *Asian J. Chem.*, **16**, 67 (2004).
6. J.H. Zar, Biostatistical Analysis, Pearson Education, edn. 4, p. 433 (1999).
7. M. Jaiswal, P.V. Khadikar and C.T. Supuran, *Bioorg. Med. Chem.*, **12**, 2477 (2004).
8. L.K. Son, A.K. Gupta and S.G. Kashedikar, *Indian Drugs*, 41 (2004).
9. S.V. Despande, M.A. Babu, A.K. Gupta, S.G. Kashedikar and A.K. Saxena, *Med. Chem. Res.*, **13**, 337 (2004).

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