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QSAR Analysis of Some Aryloxypropanolamine Analogues as Anticonvulsants

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ABSTRACT

Quantitative Structure Activity Relationship (QSAR) studies were conducted on aryloxypropanolamine analogues having anticonvulsant activity using combination of various electronic, steric, thermodynamic and topological descriptors. The van der waal energy, LUMO and connolly solvent excluded volume play significant role in anticonvulsant activity. The QSAR model was significantly improved after removal of outlier. The predictive ability of model was validated using a set of compounds that was not included in training set. These results should be applicable to the prediction of the activities of new aryloxypropanolamine analogues, as well as providing structural implications for designing potent and selective anticonvulsant agents.

Keywords: QSAR, Aryloxypropanolamine Analogues, Anticonvulsant.

INTRODUCTION

Epilepsy is the most common primary neurological disorder known [1], being one of the world's oldest recognized disorders, it is surrounded by fear, discrimination, social and frightening manifestation [2]. A global campaign against epilepsy conducted by World Health Organization (WHO) in partnership with International Bureau for Epilepsy (IBE) and International League Against Epilepsy (ILAE) suggests that around 1% of the world population at any time (about 50 million people worldwide) is affected with this neurological disorder. Every year about 2.4 million new cases are added to these figures [3, 4]. Currently available antiepileptic drugs (AEDs) provide adequate seizure control in many patients, still about 28–30% of patients are estimated to be poorly treated [5, 6]. Much efforts devoted in the recent years for the development of novel therapeutics resulted in the availability of several newer drugs (such as pregabalin, stiripentol, zonisamide, tiagabine, lamotrigine, levetiracetam, topiramate) as promising anticonvulsants [7-9]. These drugs have proven to be effective in reducing seizure, whilst their therapeutic efficacy is overcome by some

undesirable side effects such as headache, nausea, hepatotoxicity, anorexia, ataxia, drowsiness, gastrointestinal disturbances and hirsutism [10,11].

These observations affirm the search of safer and more potent anticonvulsant medications which remains a drug design priority [12,13]. Quantitative Structure Activity Relationship (QSAR) studies have received widespread attention as a powerful drug design tool for the optimization of promising drug candidates [14-19].

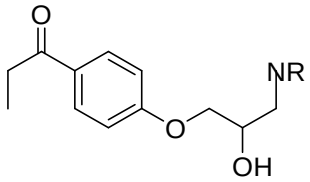
In the present study, QSAR methodology was used to elucidate the structural correlation of anticonvulsant activity in a series of aryloxypropanolamine analogues which have been shown to possess anticonvulsant activity. The predictive ability of each of our optimized model was evaluated using test set of 12 compounds that were not included in the model.

MATERIALS AND METHODS

2.1 Data Set and Biological Activity:

The training and test sets used to comprise a series of aryloxypropanolamine analogues which exhibits anticonvulsant activity. The ED_{50} values (mg/kg), were converted to negative logarithmic dose in µM/kg (-log ED_{50}) values, because QSAR study is a linear free energy relationship and from the van't Hoff isotherm, free energy change during a process is proportional to the logarithm of the rate or equilibrium constant of the process (ΔG = -2.303 RT log K). Training set (27 compounds) and the test set (12 compounds) were selected by considering the fact that the test set compounds represents structural diversity and a range of biological activities similar to that of training set.

Table-1. Structure and Anticonvulsant Activity of Aryloxypropanolamine Analogues.

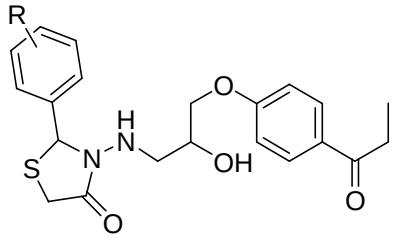


Sr. No	Compound No	R	ED $_{50}$ (mg/kg)
1	**T-1**	morpholino	32.4
2	**TR-1**	piperidino	100
3	**T-2**	peperazino	52
4	**TR-2**	imidazolino	73.4
5	**TR-3**	pyrrolidino	81.8
6	**TR-4**	dimethylamino	152
7	**TR-5**	diethylamino	120
8	**T-3**	phenylamino	34
9	**T-4**	diphenylamino	89.6
10	**TR-6**	4-hydroxyphenylamino	75.2
11	**TR-7**	4-bromophenylamino	31
12	**TR-8**	4-nitrophenylamino	131
13	**TR-9**	4-fluorophenylamino	161
14	**TR-10**	4-methylphenylamino	43.9
15	**TR-11**	4-ethoxyphenylamino	152

Compounds in test set allowed us to use one test compounds per two training compounds thus resulting in more rigorous validation of the training model. In addition, a wide range of structural diversity of compounds in the test set permit us to evaluate the extrapolative accuracy of the QSAR models. The mean (SD) of the anticonvulsant activity (-log ED_{50}) in

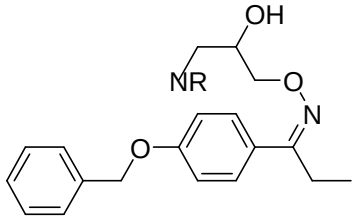
the training set and the test set were 3.652 (0.30) and 3.716 (0.25), respectively, which confirms the test set as a true representative of training set. The structures of the compounds in the training and test sets are shown in **Table- 1, 2 and 3**.

Table-2. Structure and Anticonvulsant Activity of Aryloxypropanolamine Analogues.



Sr. No	Compound No	R	ED $_{50}$ (mg/kg)
16	**TR-12**	phenyl	104
17	**T-5**	4-chlorophenyl	34.8
18	**T-6**	4-nitrophenyl	131
19	**TR-13**	2,4-dichlorophenyl	29.3
20	**T-7**	4-hydroxyphenyl	157
21	**TR-14**	3, 4-dihydroxyphenyl	131
22	**T-8**	4-methoxyphenyl	145
23	**T-9**	4-fluorophenyl	43.5
24	**TR-15**	4-bromophenyl	50.2
25	**TR-16**	2,4-dinitrophenyl	156

Table-3. Structure and Anticonvulsant Activity of Aryloxypropanolamine Analogues



Sr. No	Compound No	R	ED $_{50}$ (mg/kg)
26	**TR-17**	morpholino	31
27	**TR-18**	piperidino	46.3
28	**T-10**	peperazino	53.1
29	**TR-19**	imidazolino	28
30	**T-11**	pyrrolidino	129
31	**TR-20**	dimethylamino	154
32	**T-12**	diethylamino	131
33	**TR-21**	phenylamino	161
34	**TR-22**	4-hydroxyphenylamino	131
35	**TR-23**	4-bromophenylamino	36.6
36	**TR-24**	4-nitrophenylamino	128
37	**TR-25**	4-fluorophenylamino	45.7
38	**TR-26**	4-methylphenylamino	160
39	**TR-27**	4-ethoxyphenylamino	133

2.2 Molecular Modeling:

The QSAR computations were carried out using ChemOffice software [20]. All the molecules were drawn and converted to 3D structures in ChemDraw module. Energy minimization were performed using the MMFF94 force field [21], followed by AM-1 (Austin Model-1) Hamiltonian method, closed shell restricted wave function available in MOPAC

module with the convergence criterion 0.001 kcal/mol Å. Twenty eight descriptors were calculated for energy minimized and geometrically optimized structures which are given in **Table-4**.

Table-4. Descriptors Calculated for QSAR Study.

Sr. No.	Descriptors	Type
1	Heat of Formation (HF)	Thermodynamic
2	Log P	Thermodynamic
3	Molar Refractivity (MR)	Thermodynamic
4	Bend Energy (Eb)	Thermodynamic
5	Non–1, 4 VDW Energy (NVDWE)	Thermodynamic
6	Stretch Energy (SE)	Thermodynamic
7	Stretch–Bend Energy (SBE)	Thermodynamic
8	Torsion Energy (TSE)	Thermodynamic
9	Total Energy (TE)	Thermodynamic
10	VDW 1,4 Energy (VDE)	Thermodynamic
11	Connolly Accessible Area (CAA)	Steric
12	Connolly Molecular Area (CMA)	Steric
13	Connolly Solvent–Excluded Volume (CSEV)	Steric
14	Ovality	Steric
15	Principal Moment of Inertia – X (PMI–X)	Steric
16	Principal Moment of Inertia – Y (PMI–Y)	Steric
17	Principal Moment of Inertia – Z (PMI–Z)	Steric
18	Winner Index (WI)	Topological
19	Total Connectivity (Tc)	Topological
20	Radius(R)	Topological
21	Molecular Topological Index(MTI)	Topological
22	Cluster Count (Cc)	Topological
23	Balaban Index (BIndex)	Topological
24	Repulsion Energy (Re)	Electronic
25	LUMO	Electronic
26	HOMO	Electronic
27	Electronic Energy (EE)	Electronic
28	Dipole (D)	Electronic

In order to generate QSAR models sequential multiple regression analysis were performed using *VALSTAT* program [22]. The statistical qualities of the equations [23], were judged by the parameters like explained variance (r^2), correlation coefficient (r), standard error of estimate (*SEE*) and variance ratio (F). All accepted equations have regression coefficients and F ratios significant at 95% and 99% levels, respectively, if not stated otherwise. All the generated models were validated by *PRESS* (leave-one-out) [24,25], cross-validated r^2 (q^2), predicted residual sum of squares (*PRESS*), standard deviation based on *PRESS* (S_{PRESS}), standard deviation of error of prediction (S_{DEP}) and bootstrap r^2 (r^2bsp). Definitions of some of the statistical terms are given below.

Coefficient of determination (r): This is the most commonly used term to describe the goodness of fit of data for a regression model. This statistic is defined in the following equation:

$$r = \sqrt{1 - \frac{\sum (Ycal - Y)^2}{\sum (Y - \bar{Y})^2}} \qquad \text{(Eqn. 1)}$$

In Eqn.1, Y_{calc} and Y indicate calculated and observed activity values, respectively, and $\bar{Y}$ indicates mean activity value.

Explained variance (r^2): Explained variance of the training set without validation may be defined as follows:

$$r^2 = \sqrt{\frac{(n-1)R^2 - P}{n - P - 1}} \qquad \text{(Eqn.2)}$$

In Eqn. 2, r^2 is squared correlation coefficient, P is number of predictor variables and n is number of compounds.

Variance ratio (F): It gives an indication about the stability of the regression coefficients.

$$F = \frac{\frac{\sum (Y_{cal} - \bar{Y})^2}{P}}{\frac{\sum (Y_{cal} - Y)^2}{n - P - 1}} \qquad \text{(Eqn. 3)}$$

Standard error of estimate (SEE): This is defined as,

$$SEE = \sqrt{\frac{\sum (Y_{cal} - Y)^2}{n - P - 1}} \qquad \text{(Eqn. 4)}$$

Cross-validated r^2 (q^2): It measures predictive r^2 (leave-one-out) and part of the variance explained in the validation data.

$$q^2 = 1 - \frac{\sum (Y_{pred} - Y)^2}{\sum (Y - \bar{Y})^2} \qquad \text{(Eqn. 5)}$$

In Eqn. 5, Y_{pred} and Y indicate predicted and observed activity values, respectively and $\bar{Y}$ indicates mean activity value.

PRESS: It is the predicted residual sum of squares, the difference between predicted and the calculated values.

$$PRESS = (Y_{pred} - Y)^2 \qquad \text{(Eqn. 6)}$$

Standard deviation of error of prediction (S_{DEP}): S_{DEP} is a measure of prediction of error.

$$S_{DEP} = \sqrt{\frac{PRESS}{n}} \qquad \text{(Eqn.7)}$$

S_{PRESS}*:* Standard deviation based on *PRESS* is defined as:

$$S_{PRESS} = \sqrt{\frac{PRESS}{n-P-1}} \qquad \text{(Eqn.8)}$$

Bootstrap r^2: This is the average squared correlation coefficient calculated during the validation procedure (leave-one-out). The models derived on training set compounds were also validated through the external validation using the parameters like r^2_{pred} and r^2_{test}.

r^2_{pred} : The predictive r^2 was based only on molecules present in the test set and is defined as:

$$r^2_{pred} = 1 - \frac{\sum (Y_{pred(test)} - Y_{(test)})^2}{\sum (Y_{(test)} - \overline{Y}_{(training)})^2} \qquad \text{(Eqn. 9)}$$

In Eqn. 9, $Y_{pred}(test)$ and $Y(test)$ indicate predicted and observed activity values, respectively, of the test set compounds and Y training indicates mean activity value of the training set. The r^2 test is the squared correlation coefficient (r^2) between the observed and predicted data of the test set. Randomization test at 99% confidence level was carried out for the selected models. The acceptability criteria of a valid QSAR model include a q^2 value of more than 0.5 and a difference of $q2$ and r^2 value being less than 0.3 [26]. The external validation is a more reliable way to establish a predictive QSAR model [27]. When the data set is divided into training and test sets and a model is generated based on the training set compounds, the r^2_{pred} value should be more than 0.5

RESULTS AND DISCUSSION

The Aryloxypropanolamine analogues was divided into training set of 27 compounds and test set of 12 compounds (**Table-1, 2 and 3**), on the basis of structural diversity and complete range of variation in biological activity. The training set was subjected to sequential multiple linear regression analysis in order to establish correlation between physicochemical parameters and anticonvulsant activity.

-log ED$_{50}$ = [3.077(±0.389)] + ***Re*** [-0.002(±0.001)] + ***LUMO*** [0.055(±0.025)] + ***EE*** [-0.0015 (± 0.0011)] (**Model. 1**)

n = 27, ***r*** = 0.769, $\boldsymbol{r^2}$ = 0.593, ***Variance*** = 0.042, ***SEE*** = 0.205, ***F*** = 11.15, $\boldsymbol{r^2_{bsp}}$ = 0.607, ***Chance*** = <0.001, $\boldsymbol{q^2}$ = 0.506, $\boldsymbol{S_{PRESS}}$ = 0.226, $\boldsymbol{S_{DEP}}$ = 0.208, $\boldsymbol{r^2_{pred}}$ = 0.546

The Model-1 accounts for more than 59.3% of the variance in the activity with a correlation coefficient (r = 0.769). The value of sequential Fischer test suggest more than 99.9% internal statistical significance as it exceeds the tabulated value F = 11.15. The inter-correlation among the parameters (ICAP) is ≤ 0.99 (**Table-9**), which suggests that all parameters

contribute individually and independently to the model. The absence of outlier suggests that the selected model is able to explain structural diversity in the congeners. The selected model was further statistically evaluated to confirm its robustness. The cross-validated squared correlation coefficient (q^2 = 0.506), predictive residual sum of square (S_{PRESS} = 0.226) and standard error of prediction (S_{DEP} = 0.208) suggested good internal consistency as well as predictive ability of the biological activity (**Table-5 and 6**). The value of the bootstrapping squared correlation coefficient (r^2_{bsp} = 0.607) is at par with the conventional squared correlation coefficient (r^2 = 0.593), suggest that no single compound contribute too low or too high an extent, indicating that model can be used for wide range of structural analogs. Plots of observed (-log ED_{50}) verses calculated and predicted (LOO) (-log ED_{50}) with residuals for training set using model-1 are shows in **Figure-1 and 3**, respectively.

Table-5. Observed, Calculated, Predicted (LOO), Z-score and Residuals Considering Model-1

Sr. No.	-log ED_{50} [a]	-log ED_{50} [b]	R [c]	-log ED_{50} [d]	R [e]	Z-Score
TR-1	3.4644	3.4827	-0.0183	3.4845	-0.0201	-0.0972
TR-2	3.5725	3.4725	0.1	3.4585	0.114	0.516
TR-3	3.5299	3.477	0.0529	3.4716	0.0583	0.2656
TR-4	3.2183	3.4573	-0.239	3.4999	-0.2816	-1.2418
TR-5	3.3671	3.4812	-0.1141	3.4944	-0.1273	-0.593
TR-6	3.6226	3.5317	0.0909	3.5244	0.0982	0.4684
TR-7	4.0861	4.092	-0.0059	4.1153	-0.0292	-0.0315
TR-8	3.4197	3.5609	-0.1412	3.5699	-0.1502	-0.7365
TR-9	3.2947	3.5538	-0.2591	3.5751	-0.2804	-1.3486
TR-10	3.8536	3.5108	0.3428	3.4825	0.3711	1.7754
TR-11	3.3539	3.2513	0.1026	3.2131	0.1408	0.5276
TR-12	3.5855	3.5928	-0.0073	3.5932	-0.0077	-0.0408
TR-13	4.2048	3.666	0.5388	3.6231	0.5817	2.7917
TR-14	3.5187	3.6591	-0.1404	3.671	-0.1523	-0.7323
TR-15	3.9799	3.6165	0.3634	3.5935	0.3864	1.8807
TR-16	3.4975	3.6582	-0.1607	3.7108	-0.2133	-0.8366
TR-17	4.1091	4.1741	-0.065	4.2071	-0.098	-0.3379
TR-18	3.9326	3.9837	-0.0511	3.9949	-0.0623	-0.2684
TR-19	4.1319	3.9747	0.1572	3.9446	0.1873	0.8107
TR-20	3.3644	3.5706	-0.2062	3.58	-0.2156	-1.0721
TR-21	3.4001	3.6256	-0.2255	3.6379	-0.2378	-1.1711
TR-22	3.5065	3.4743	0.0322	3.4701	0.0364	0.1641
TR-23	4.1209	4.153	-0.0321	4.1654	-0.0445	-0.1713
TR-24	3.5455	3.6588	-0.1133	3.6733	-0.1278	-0.5906
TR-25	3.9659	3.7832	0.1827	3.7714	0.1945	0.9432
TR-26	3.4176	3.4509	-0.0333	3.4555	-0.0379	-0.1758
TR-27	3.5279	3.6614	-0.1335	3.6781	-0.1502	-0.6979

[a] *Observed Biological Activity,* [b] *Calculated Biological Activity,* [c] *Residuals Considering Calculated Activity,* [d] *Predicted Biological Activity,* [e] *Residuals Considering Predicted Activity*

Randomized biological activity test (*Chance* < 0.01) revealed that results were not based on chance correlation. The test data set gave significant predictive correlation coefficient (r^2_{pred} = 0.546). Plot of observed (-log ED_{50}) verses predicted (LOO) (-log ED_{50}) with residuals for test set using model-1 is shown in **Figure-5**.

Model-1 revealed that LUMO (Lower Unoccupied Molecular Orbital) energy contributes positively while repulsion energy and electronic energy has negative contribution in biological activity. LUMO is a rough measure of the electron-accepting ability of a compound and normally, reducing its value raises up that ability. The repulsive energy is a representative of repulsion field which is measure of the energy required to keep two electrons each on separate π atoms and the energy required to keep two electrons, occupying the same orbital on the same π atom, from moving apart. The repulsive field is as sign of electronegativity of moiety. The negative contribution of repulsion energy shows that substitution of electron donating group is favorable for ligand and receptor interactions and biological activity. Electronic energy is represents electronic descriptors which deduce the electronic chemical potential how energetically favorable to accept electrons, the negative contribution of electronic energy shows that electron donating groups may favorable for anticonvulsant activity.

Table-6. Observed, Calculated, Predicted (LOO), Z-score and Residuals Considering Model-1

Sr. No.	-log ED_{50}[a]	-log ED_{50}[b]	Residuals
T-1	3.9568	3.511	0.4458
T-2	3.7499	3.496	0.2539
T-3	3.9447	3.4927	0.452
T-4	3.6222	3.5532	0.069
T-5	4.0996	3.6244	0.4752
T-6	3.5315	3.2282	0.3033
T-7	3.4237	3.6281	-0.2044
T-8	3.4726	3.6424	-0.1698
T-9	3.9831	3.6432	0.3399
T-10	3.8742	3.6098	0.2644
T-11	3.472	3.5962	-0.1242
T-12	3.4676	3.5964	-0.1288

[a] *Observed Biological Activity,* [b] *Predicted Biological Activity.*

-log ED$_{50}$ = [3.306(±0.587)] + ***LUMO*** [0.063(±0.029)] + ***VDE*** [-0.050(±0.043)] + ***CSEV*** [0.003(± 0.002)]

n = 27, ***r*** = 0.731, r^2 = 0.534, ***Variance*** = 0.048, ***SEE*** = 0.219, ***F*** = 8.79 (**Model. 2**)

The development of significant equation with three different types of physicochemical descriptors yields Model-2 with correlation coefficient (*r* = 0.731). The data showed overall internal statistical significance level as *F* = 8.79. The model was further analyzed for search of outliers and two outliers namely compound nos. TR-7 and TR-13 were detected from their z-score values.

-log ED$_{50}$ = [3.247(±0.458)] + ***LUMO*** [0.064(±0.022)] + ***VDE*** [-0.035(±0.034)] + ***CSEV*** [0.002(±0.0026)] (**Model. 3**)

n = 25, ***r*** = 0.828, ***r^2*** = 0.685, ***Variance*** = 0.027, ***SEE*** = 0.165, ***F*** =15.24, ***r$^2_{bsp}$*** = 0.699, ***Chance*** = <0.001, ***q^2*** = 0.563, ***S$_{PRESS}$*** = 0.195, ***S$_{DEP}$*** = 0.179, ***r$^2_{pred}$*** = 0.625

Further development of model-2, omission of these outliers improves the statistical qualities gave model-3, has a correlation coefficient (r = 0.828) which accounted for more than 68.5% of the variance in the activity. The equation shows that in the multi-variant model, the dependant variable can be predicted from a linear combination of the independent variables. The data showed overall internal statistical significance level better than 99.99 % as it exceeds the tabulated F = 15.24. The cross-validated squared correlation coefficient (q^2 = 0.563), predictive residual sum of square (S_{PRESS} = 0.195) and standard error of prediction (S_{DEP} = 0.179) suggested good internal consistency as well as predictive ability of the biological activity (**Table-7 and 8**).

The r^2_{bsp} is at par with the conventional squared correlation coefficient (r^2). Plots of observed (-log ED$_{50}$) verses calculated and predicted (LOO) (-log ED$_{50}$) with residuals for training set using model-1 are shows in **Figure-2 and 4**, respectively. Randomized biological activity test (*Chance* < 0.001) revealed that results were not based on chance correlation. The inter-correlation among the parameters is less than 0.78 (**Table-10)**. The test data set gave significant predictive correlation coefficient (r^2_{pred} = 0.625). Plot of observed (-log ED$_{50}$) verses predicted (LOO) (-log ED$_{50}$) with residuals for test set using model-1 are shows in **Figure.6**.

The model-3 shows that LUMO energy and Connolly Solvent Excluded Volume (CSEV) contributes positively while van der waals energy contributes negatively to anticonvulsant activity. LUMO energy is an electronic descriptor which is indicative of the energy of lowest unoccupied molecular orbital. It governs the molecular properties, reactivity and also measures the electrophilicity of the molecule, the positive contribution of LUMO energy is indicative that electron donating groups impart the positive influence on anticonvulsant activity.

The Connolly surface, also called the molecular surface, is similar to the solvent-accessible surface. Using a small spherical probe to simulate a solvent, it is defined as the surface made by the contact of the solvent sphere with the van der Waals surface. The volume enclosed by the Connolly surface is called the solvent-excluded volume and defined as the volume contained within the contact molecular surface. Connolly Solvent Excluded Volume (CSEV) a steric descriptor. The descriptor bears positive coefficient in the model-3, suggesting increase in the bulkiness of the substituent's is conducive to the activity. The Van der waals energy is a thermodynamic parameter which can be defined as the sum of pair wise Van der waals interaction energy terms for atoms separated by exactly three chemical bonds, related to the structure of the molecule itself.

The coefficient of the descriptor VDE bears a negative contribution in the model-3 which indicates that decrease in the VDE between atoms separated by 3 chemical bonds is conducive to the anticonvulsant activity.

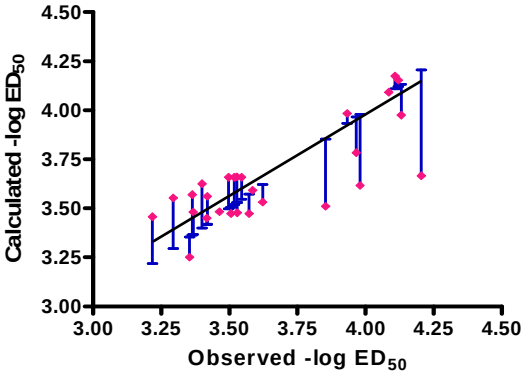


Figure-1 Graphical Representation of Observed and Calculated (-log ED_{50}) with Residual Presentation using Model-1 (Training Set).

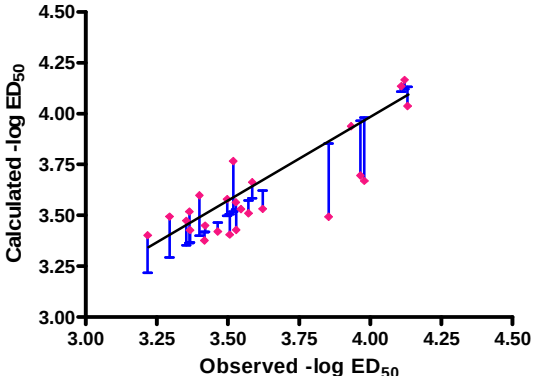


Figure-2 Graphical Representation of Observed and Calculated (-log ED_{50}) with Residual Presentation using Model-3 (Training Set).

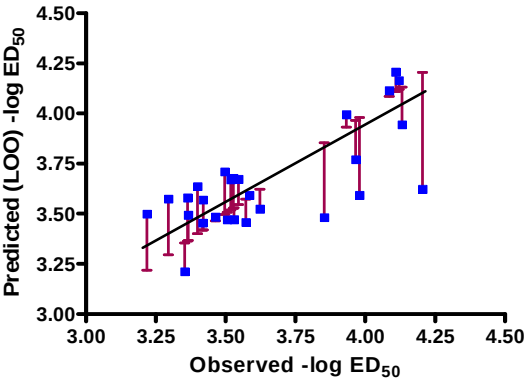


Figure-3 Graphical Representation of Observed and Predicted (LOO) (-log ED_{50}) with Residuals Presentation using Model-1 (Training Set).

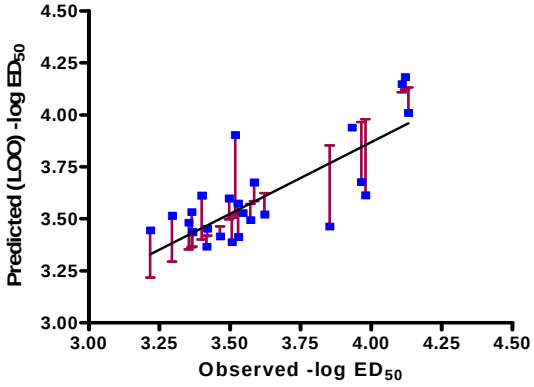


Figure-4 Graphical Representation of Observed and Predicted (LOO) (-log ED_{50}) with Residuals Presentation using Model-3 (Training Set).

Table-7 Observed, Calculated, Predicted (LOO), Z-score and Residuals Considering Model-3

Sr. No.	-log $ED_{50}{}^{a}$	-log $ED_{50}{}^{b}$	R^{c}	-log $ED_{50}{}^{d}$	R^{e}	Z-value
TR-1	3.4644	3.4213	0.0431	3.4158	0.0485	0.2747
TR-2	3.5725	3.5105	0.062	3.4949	0.0775	0.3959
TR-3	3.5299	3.4288	0.1011	3.4142	0.1156	0.6452
TR-4	3.2183	3.4025	-0.1842	3.4453	-0.227	-1.1891
TR-5	3.3671	3.4283	-0.0612	3.4367	-0.0697	-0.3955
TR-6	3.6226	3.5319	0.0907	3.5223	0.1026	0.5802
TR-7*	4.0861	-	-	-	-	-
TR-8	3.4197	3.4507	-0.031	3.4532	-0.0335	-0.2043
TR-9	3.2947	3.4943	-0.1996	3.5158	-0.2211	-1.291
TR-10	3.8536	3.4937	0.3599	3.4649	0.3886	2.3154
TR-11	3.3539	3.4741	-0.1202	3.4828	-0.1289	-0.781
TR-12	3.5855	3.664	-0.0785	3.6759	-0.0904	-0.5093
TR-13*	4.2048	-	-	-	-	-

TR-14	3.5187	3.7667	-0.248	3.9053	-0.3866	-1.6031
TR-15	3.9799	3.6694	0.3105	3.6144	0.3654	1.9956
TR-16	3.4975	3.5801	-0.0826	3.5993	-0.1018	-0.5358
TR-17	4.1091	4.1354	-0.0263	4.1494	-0.0404	-0.1705
TR-18	3.9326	3.9379	-0.0053	3.9396	-0.007	-0.0383
TR-19	4.1319	4.0374	0.0945	4.0109	0.1209	0.6032
TR-20	3.3644	3.519	-0.1546	3.5336	-0.1692	-0.9992
TR-21	3.4001	3.5984	-0.1983	3.6133	-0.2132	-1.2789
TR-22	3.5065	3.4055	0.101	3.3886	0.1179	0.6475
TR-23	4.1209	4.1654	-0.0445	4.1837	-0.0628	-0.2927
TR-24	3.5455	3.5313	0.0142	3.5287	0.0167	0.0902
TR-25	3.9659	3.6964	0.2695	3.6784	0.2874	1.731
TR-26	3.4176	3.3771	0.0405	3.3671	0.0504	0.257
TR-27	3.5279	3.5653	-0.0374	3.5753	-0.0474	-0.2469

*[a] Observed Biological Activity, [b] Calculated Biological Activity, [c] Residuals Considering Calculated Activity, [d] Predicted Biological Activity, [e] Residuals Considering Predicted Activity, * Compound was Found as Outlier.*

Table-8 Observed, Calculated, Predicted (LOO), Z-score and Residuals Considering Model-3

Sr. No.	-log ED_{50}[a]	-log ED_{50}[b]	Residuals
T-1	3.9568	3.39165	0.56515
T-2	3.7499	3.433	0.3169
T-3	3.9447	3.47601	0.46869
T-4	3.6222	3.4727	0.1495
T-5	4.0996	3.66657	0.43303
T-6	3.5315	3.59571	-0.06421
T-7	3.4237	3.71207	-0.28837
T-8	3.4726	3.64353	-0.17093
T-9	3.9831	3.6583	0.3248
T-10	3.8742	3.52434	0.34986
T-11	3.472	3.53001	-0.05801
T-12	3.4676	3.51586	-0.04826

[a]Observed Biological Activity, [b] Predicted Biological Activity,

Quantitative Structure Activity Relationship is widely used technique not only because it is not very computationally intensive but also it leads to the rapid generation of models from which the biological activities of newly designed compounds can be predicted. A high correlation coefficient merely not enough to select the equation as the model. Equations were screened through various internal and external statistical validation techniques. Internal statistical significance level of the equations was confirmed using sequential Fischer test, all the equations have significance level more than 99.9%. Sequential Fischer test recommended that equations are applicable for more than 999 times out of 1000. The inter dependency of physicochemical parameters for each equation was checked in order to confirm inimitable contribution of the properties to the expression. All the regression expressions were checked for the presence of outliers using *Z*-score method. This test confirms the applicability of

equation on structurally diverse analogs. In the case of Model-2, two outliers were present. The presence of outliers reveled that physicochemical properties involved in Model-2 are not factual representative for prediction of structurally diverse analogues.

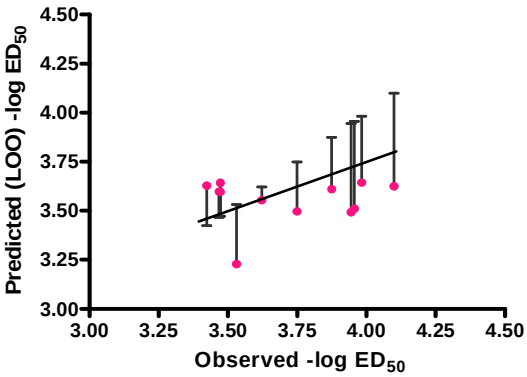


Figure-5 Graphical Representation of Observed and Predicted (LOO) (-log ED_{50}) with Residuals Presentation using Model-1 (Test Set).

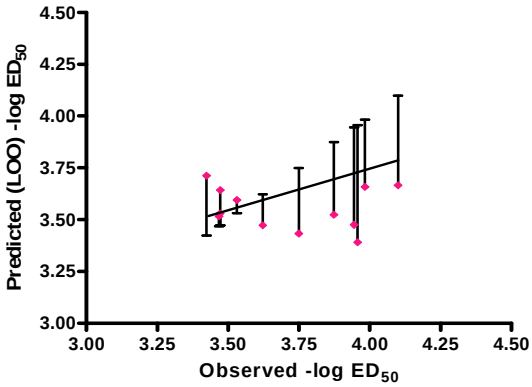


Figure-6 Graphical Representation of Observed and Predicted (LOO) (-log ED_{50}) with Residuals Presentation using Model-3 (Test Set).

Table-9 Correlation Matrix (Model-1)

Descriptors	Re	LUMO	EE
Re	1.000		
LUMO	0.146	1.000	
EE	0.995	0.136	1.000

Table-10 Correlation Matrix (Model-3)

Descriptors	LUMO	VDE	CSEV
LUMO	1.000		
VDE	0.421	1.000	
CSEV	0.266	0.786	1.000

Bootstrapping techniques was employed to confirm the contribution of physicochemical properties of the molecules to the activity weather equi-intense or of different rank. The value of the bootstrapping squared correlation coefficient and bootstrapping standard deviation implies that the equation were proper representative of the group of analogues. The chance of fortuitous correlation was checked with help of randomized biological activity test, the value of chance statistic is less than 0.001. Data of chance statistic revealed that the results were not based on chance correlation. The internal consistency of training set was confirmed by leave-one-out method of cross-validation. Although model-1 and 3 showed good internal consistency (q^2 = 0.506 and 0.563, respectively), they may not be applicable for the analogs, which were never used in the generation of correlation. Therefore, the predictive power of model-1 and 3 was further confirmed by a test set of 12 compounds showed (r^2_{Pred} = 0.546 and 0.625, respectively), the r^2_{Pred} values revealed robustness and wide applicability of these models. The statistical validation criteria is to the significant extent and therefore would be considered as models for designing more active compounds.

CONCLUSION

The 2D-QSAR study of 39 aryloxypropanolamine analogues having anticonvulsant activity was carried out using molecular modeling program ChemOffice version. A high bootstrapped r^2 value for QSAR models with a small *SEE* indicated the existence of similar relationship among all of the compounds used to build QSAR model. In addition LUMO (lower unoccupied molecular orbital), Connolly Solvent Excluded Volume (CSEV) and van der waal (VDE) energy were found to be important for anticonvulsant activity as exemplified by the higher predictive power of the QSAR model. the results obtained from 2D-QSAR models

were found to accurately predict the anticonvulsant activity of structurally diverse test set compounds and to yields reliable clues for further optimization of the aryloxypropanolamine analogues in the data set

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