Research Article

2D QSAR STUDY OF SOME INHIBITORS OF EHRLICH ASCITES CARCINOMA

Subrata Sen*, Koushik Sarker
*A. P. C. Ray Memorial Cancer Chemotherapeutic Research Unit, College of Pharmaceutical Sciences, Mohuda, Berhampur, Orissa, India.
*Corresponding author's E-mail: ccru_cps@rediffmail.com

Accepted on: 18-06-2012; **Finalized on:** 31-07-2012.

ABSTRACT

Several glutamic acid analogs were designed, synthesized and evaluated *in vivo* on EAC cells. With the ligand-based approach, it is necessary to develop a 2D QSAR model, which can beacon cue on further design to help invent most active molecule of the series. 80 congeneric molecules were selected, with meaningful descriptor and justified by befitting statistical parameters. The principle of parsimony was applied. Nearly 120 descriptors from TSAR 3.3 and CHEM DRAW ULTRA 12.0 were generated and MLR was performed to develop the model using TSAR 3.3 and SIGMAPLOT 11.0. A significant r (0.862), r^2 (0.743), r^2CV (0.707) was obtained. The model was validated externally r^2 (0.694).

Keywords: 2D QSAR, MLR, Glutamic Acid, EAC, TSAR3.3.

INTRODUCTION

Until now several glutamic acid analogs as esters, amines, amides and hydrazides have been synthesized in our laboratory by bioisosteric replacement of metabolite structure of thalidomide and tested on EAC for anticancer activity. In the year 1964, an endeavor to correlate quantitatively biological activity and chemical structures were made.[1] A few Physicochemical parameters, i.e. lipophilicity, expressed by log P or π values, electronic properties, expressed by σ, molar refractivity MR, steric properties, and/or parabolic lipophilicity terms were used in the correlations. Development in quantum chemical and geometrical parameters, connectivity values, electrotopological state parameters, and many others allowed drug designers to explicate SARs in a quantitative mode and to predict the activities of new analogs[2,3].

To develop a significant QSAR model 80 congeneric molecule was selected, with meaningful descriptor and justified by befitting statistical parameters. The principle of parsimony was applied, i.e. results are approximately equal, the simplest model must be selected, and too many variables should not be tested and included in the final model.[4] The descriptors from TSAR 3.3 and CHEM DRAW ULTRA 12.0 were generated and MLR was performed to develop the model using TSAR 3.3 and SIGMAPLOT 11.0.

MATERIALS AND METHODS

Data set for analysis

The *in vivo* biological activity data reported as percentage inhibition was converted to log BA (biological activity) for inhibition of Ehrlich ascites carcinoma cell by a series of glutamic acid derivatives.

As a rule, 66 compounds added as a TRAINING set (dependent variable) for the QSAR study along with 14 compounds as TEST set, to test the predictive ability of the model generated.

Structure preparation and descriptor calculation

Three-dimensional structure of all molecules along with Partial charge was calculated using the Charge-2 CORINA 3D package in TSAR 3.3, and the inhibitor geometries were optimized using its Cosmic Module. The utility of Charge-2 is depended on two fundamental chemical concepts:

a) The inductive effect in saturated molecules

b) Huckle molecular orbital calculations (HMO) for π-systems.

Molecular descriptors for the substituents were calculated, which vary in common points of the generic structure as shown in table 1.

Several Topological, Connectivity, Shape indices, Hydrophobic and Thermodynamic descriptors were generated to describe our samples. With whole molecule and three substituents, altogether 120 descriptors (independent variables) were calculated. This gives a very large data set, which may increase the risk of over fitting the data. To circumvent this problem pruning of data was carried out which helped in reducing data redundancy that could lead to low Predictability of the model. Descriptors with the same values for all the compounds were discarded (due to zero variance).[5] For further data reduction, a correlation matrix was generated to study the data pattern. Data was reduced by pair wise correlation.[6] Among the highly inter-correlated descriptors, the one that had a high correlation with biological activity were retained and the other was discarded. Through iterative processes, eventually 26 descriptors were chosen, which are non-correlated with each other.

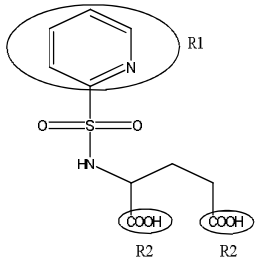


Table 1: Data set for training compounds (R2= R3)

Entry Number	R1	R2	% Inhibition	Observed logBA	Predicted logBA	Residual value
X1	Benzene	—COOH	15.47	1.1895	1.20243	-0.01293
X2	Benzene	—$COOCH_3$	28.21	1.45054	1.47649	-0.02595
X3	Benzene	—$COOCH_2CH_3$	37.83	1.57786	1.56026	0.0176
X4	Benzene	—$CONHNH_2$	31.71	1.50123	1.51685	-0.01562
X5	Benzene	—$CONHNHC_6H_5$	34.602	1.53911	1.55296	-0.01385
X6	Benzene	—CONHNH–Cl	56.5	1.75208	1.61281	0.13927
X7	Benzene	—CONHNH–CH_3	39.38	1.595	1.61565	-0.02065
X8	Benzene	—CONHNH–NO_2	34.087	1.5326	1.6252	-0.0926
X9	Benzene	—CONHNH (O_2N)	36.69	1.56455	1.6422	-0.07765
X10	4-Methoxy benzene	—COOH	57.18	1.70915	1.56503	0.14412
X11	4-Methoxy benzene	—$COOCH_3$	38.77	1.5885	1.65539	-0.06689
X12	4-Methoxy benzene	—$COOCH_2CH_3$	36.62	1.56374	1.65452	-0.09078
X13	4-Methoxy benzene	—$CONHNHC_6H_5$	45.76	1.66058	1.68412	-0.02354
X14	4-Methoxy benzene	—CONHNH–Cl	47.53	1.67702	1.58136	0.09566
X15	4-Methoxy benzene	—CONHNH–CH_3	38.89	1.58993	1.59373	-0.0038
X16	4-Methoxy benzene	—CONHNH–NO_2	51.98	1.71586	1.68993	0.02593
X17	4-Methoxy benzene	—CONHNH (O_2N)	46.06	1.6634	1.68993	-0.02653
X18	3, 4-Dimethoxy benzene	—COOH	55.54	1.74466	1.69659	0.04807
X19	3, 4-Dimethoxy benzene	—$COOCH_3$	39.97	1.60178	1.66163	-0.05985
X 20	3, 4-Dimethoxy benzene	—$COOCH_2CH_3$	49.59	1.69541	1.70205	-0.00664
X21	3, 4-Dimethoxy benzene	—$CONHNH_2$	34.45	1.5372	1.69193	-0.15473
X22	3, 4-Dimethoxy benzene	—$CONHNHC_6H_5$	58.91	1.7702	1.62203	0.14817
X23	3, 4-Dimethoxy benzene	—CONHNH–Cl	46.65	1.6689	1.578	0.0909
X24	3, 4-Dimethoxy benzene	—CONHNH–NO_2	27.62	1.4413	1.62586	-0.18456
X25	3, 4-Dimethoxy benzene	—CONHNH (O_2N)	46.51	1.66762	1.6395	0.02812
X26	4-Ethoxy benzene	—COOH	57.33	1.75839	1.6217	0.13669
X27	4-Ethoxy benzene	—$COOCH_3$	50.51	1.7034	1.7285	-0.0251
X28	4-Ethoxy benzene	—$COOCH_2CH_3$	55.36	1.7432	1.77359	-0.03039
X29	4-Ethoxy benzene	—$CONH_2$	38.82	1.5891	1.62659	-0.03749
X30	4-Ethoxy benzene	—$CONHCH_3$	42.32	1.6266	1.64573	-0.01913
X31	4-Ethoxy benzene	—$CONHCH_2CH_3$	61.26	1.78721	1.69827	0.08894
X32	4-Ethoxy benzene	—$CONHCH_2CH_2CH_3$	46.15	1.66421	1.74615	-0.08194
X33	4-Ethoxy benzene	—$CONHCH(CH_3)CH_3$	54.03	1.73265	1.74665	-0.014
X34	4-Ethoxy benzene	—$CONHCH_2CH_2CH_2CH_3$	49.24	1.6924	1.73526	-0.04286
X35	4-Ethoxy benzene	—$CONHNH_2$	68.92	1.83837	1.7642	0.07417

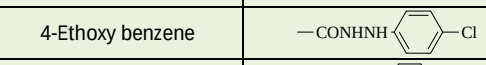
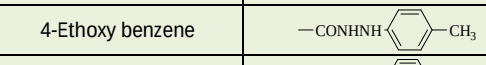
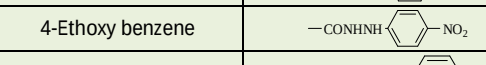
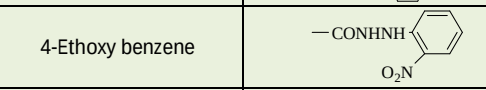
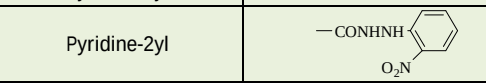
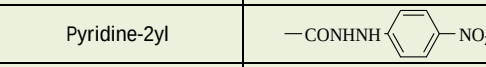
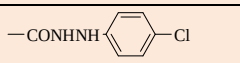
X36	4-Ethoxy benzene	—CONHNHC$_6$H$_5$	45.06	1.65385	1.78621	-0.13236
X37	4-Ethoxy benzene		68.54	1.836	1.76038	0.07562
X38	4-Ethoxy benzene		42.25	1.6259	1.75393	-0.12803
X39	4-Ethoxy benzene		49.07	1.6909	1.66681	0.02409
X40	4-Ethoxy benzene		76.73	1.885	1.69353	0.19147
B1	Pyridine-2yl	—COOH	60.16	1.77935	1.6692	0.11015
B2	Pyridine-2yl	—COOCH$_3$	62.7	1.7973	1.86319	-0.06589
B3	Pyridine-2yl	—COOCH$_2$CH$_3$	72.41	1.8598	1.77552	0.08428
B5	Pyridine-2yl	—CONH$_2$	73.41	1.8658	1.7957	0.0701
B6	Pyridine-2yl	—CONHCH$_3$	76.29	1.8825	1.85008	0.03242
B8	Pyridine-2yl	—CONHCH$_2$CH$_2$CH$_3$	75.45	1.8777	1.81493	0.06277
B11	Pyridine-2yl	—CONHC$_5$H$_{11}$	59.08	1.7715	1.82857	-0.05707
B12	Pyridine-2yl	—CONHC$_6$H$_{13}$ (n)	67.77	1.83106	1.82135	0.00971
B4	Pyridine-2yl	—CONHNH$_2$	80.14	1.9039	1.81256	0.09134
B14	Pyridine-2yl	—CONHNHC$_6$H$_5$	69.05	1.8392	1.74703	0.09217
B15	Pyridine-2yl		68.83	1.8378	1.8536	-0.0158
B16	Pyridine-2yl		83.46	1.9215	1.91017	0.01133
X53	Quinoline-8-yl	—COOH	70.194	1.8463	1.88411	-0.03781
X54	Quinoline-8-yl	—COOCH$_3$	84.27	1.9257	1.86651	0.05919
X55	Quinoline-8-yl	—COOCH$_2$CH$_3$	87.74	1.9432	1.86661	0.07659
X56	Quinoline-8-yl	—CONHCH$_2$CH$_2$CH$_3$	82.18	1.9148	1.90512	0.00968
X57	Quinoline-8-yl	—CONHCH(CH$_3$)CH$_3$	72.84	1.8624	1.9087	-0.0463
X58	Quinoline-8-yl	—CONHCH$_2$CH$_2$CH$_2$CH$_3$	59.57	1.7751	1.84067	-0.06557
X59	Quinoline-8-yl	—CONHC$_5$H$_{11}$	86.07	1.9349	1.87698	0.05792
X60	Quinoline-8-yl	—CONHC$_6$H$_{13}$ (n)	85.42	1.9316	1.98152	-0.04992
X61	Quinoline-8-yl	—CONHC$_6$H$_{11}$ (Cyclo)	95.16	1.9785	1.98206	-0.00356
X62	Quinoline-8-yl	—CONHNH$_2$	90.92	1.9587	1.97578	-0.01708
C5	Quinoline-8-yl	—CONHCH$_2$CH$_2$CH$_3$	90.77	1.95798	1.99087	-0.03289
C2	Furan-2-yl	—COOCH$_3$	66.04	1.81981	1.79092	0.02889
C3	Furan-2-yl	—CONH$_2$	25.85	1.41252	1.59101	-0.17849
C4	Furan-2-yl	—CONHCH$_2$CH$_3$	25.77	1.41123	1.57833	-0.1671

Table 2: Data for test set compounds

Entry No.	R1	R2	log BA ESTIMATED	log BA OBSERVED	Residual
B7	Pyridine-2-yl	—CONHCH$_2$CH$_3$	1.7946	1.7964	-0.0018
B9	Pyridine-2-yl	—CONHCH(CH$_3$)CH$_3$	1.7807	1.8344	-0.0237
B10	Pyridine-2-yl	—CONHCH$_2$CH$_2$CH$_2$CH$_3$	1.8897	1.8466	0.0431
B13	Pyridine-2-yl	—CONHC$_6$H$_{11}$ cyclo	1.9699	1.8854	0.0845
B17	Pyridine-2-yl		1.8632	1.8289	0.0343
X67	Benzene	—CONHCH$_2$CH$_3$	1.8545	1.8847	-0.0302
X68	Benzene	—CONHC$_6$H$_{11}$	1.9661	1.5817	0.3844
X69	4-Methoxy benzene	—CONHNH$_2$	1.9258	1.8897	0.0361
X70	4-Methoxy benzene	—CONHCH$_3$	1.6585	1.13	0.5285
X71	Benzene	—CONHCH$_3$	1.8638	1.8085	0.0553
X72	4-methyl benzene	—COOCH$_3$	1.686	1.6142	0.0718
X73	4-methyl benzene	—COOCH$_2$CH$_3$	1.76015	1.6924	0.06775
C1	Furan-2-yl	—COOH	0.7135	0.8876	-0.1741
C6	Furan-2-yl	—CONHCH$_2$CH$_2$CH$_2$CH$_3$	1.7972	1.8345	-0.0373

RESULTS AND DISCUSSION

Model development and statistical analysis

The relationship between structural parameters and biological activities were quantified by the multiple linear regressions implemented in TSAR 3.3 and SIGMA PLOT 11.0 by Systat Software, Inc. Sigma Plot for Windows. MLR is only useful when there are more observations than variables. When the converse is true, the model developed by MLR becomes statistically unreliable. TSAR uses an automated variable selection process through a two-way stepping algorithm to select variables for the regression equation. At, each step, partial F-value is calculated for each variable, as an estimate of their potential contribution to the model.

The overall F-statistics for a model is expressed as

F= Explained Mean Square/Residual Mean Square.

Partial F values are an estimation of the sequential contribution towards the F statistics for the final model. In forward stepping process, once a variable has entered the model, it cannot leave. Values for *F*-to-enter and *F*-to-leave were set to 2 and 0 respectively, which indicates that forward stepping was applied. At each step, the partial F values of all variables outside the model are calculated. If any variable has a value greater than **F to Enter,** the variable with the highest partial F value is added to the model. The process is continued until no more variables qualify to enter the model, or the required number of steps has been reached. The cross-validation analysis was performed using the leave-one-out random selection (LOO) method leaving out one row randomly over two random trials. The Correlation limit was set to 0.9. The cross-validated r^2 and conventional r^2 that resulted in the lowest error of prediction were chosen.

Predictive correlation coefficient (r^2pred): The predictive capability of the 2D-QSAR models was determined from a set of 14 compounds that were not included during model development. Structure generation, optimization, charge derivation, and all other steps of test sets were done in the same way as that of the training set compounds as described above, and their activities were calculated using the model produced by the training set.

The predictive correlation (r^2 pred), based on the test set molecules, was computed using:

r^2 pred = (SD-PRESS)/SD

Where, **SD** is the sum of squared deviations between biological activities of the test set and mean activities of the training set molecules.

The predictive residual sum of squares **(PRESS)** is the sum of squared deviations between calculated and experimental activity values for every molecule in the test set. The dataset was randomly partitioned into a training set of 66 and a test set of 14 compounds with bias given to chemical diversity in both the training and test set molecules. Despite the ambiguity of drug-receptor interaction, a model was developed which is statistically significant. Multiple regression analysis was carried out to get the best-fit equation. Six descriptors were chosen by stepwise regression analysis.

Multiple linear regressions

log BA = (±0.113) 0.978 - 0.280 (±0.0716 * STRETCH-BEND) + 0.496 (±0.0743 * OVALITY) + 0.0253 (±0.00401* LIPOLE X COMPONENT WM) + 0.0560 (±0.0221* LIPOLE X COMP. SUB1.) + 0.00533 (±0.00248* LIPOLE Y COMP. WM) + 0.0552 (±0.00925* LIPOLE Y COMP. SUB.1) + 0.0304 (±0.00833 * BOND LIPOLE SUB1.) - 0.00416(±0.00124 * DIPOLE/DIPOLE).

This represents the final possible best-fitting linear equation between the dependent variable log BA, and the independent variables.

N = 66; r = 0.862; r^2 = 0.743; r^2 (CV) /q^2 = 0.707: Standard Error of Estimate (s) = 0.087

r: Multiple regression correlation coefficients (**0.862**) are the square root of **r^2**.

r^2: The fraction of the total variance of log BA that is explained by the regression equation (**0.743**). The closer the value to 1.0, the better the regression explains log BA.

r^2= **ESS/TSS** ESS= explained sum of square of log BA and TSS = total sum of square.

Cross validation r^2 (CV): It is the cross validated equivalent of r^2. It is the key measure of the predictive power of the model.

$$r^2 (CV) = (1\text{-}PRESS) / TSS$$

's' signifies the standard error of the regression model (**0.087**). For a model with good predictive power, this is an estimate of how accurately the model will predict the test set of compounds. The 's' value is only a valid estimate of the prediction error for models with good predictive power.

Analysis of variance

	DF	SS	MS	F
Regression	8	1.261	0.158	20.620
Residual	57	0.436	0.00765	
Total	65	1.697	0.0261	

Predictive Sum of Squares: 0.500854; F probability: 3.83355 e-^{015}

Jack-knife estimate of standard error gives an idea about standard error on each regression coefficient derived from Jack-knife procedure on the final regression model.

Covariance estimate of standard error gives an estimate of the standard on each regression coefficient derived from the covariance matrix. The classical method of deriving standard error where cross validation is not involved.

t-values measure the significance of each variable that is included in the final model, in a manner analogous to the F statistics.

t-probability values are a statistical significance for t-values. As with the F statistics, a t-probability of 0.05 indicates that a variable is significant at the 95% level. In this stepwise process, these t-values can be used only as a general indicator of variable significance.

Table 3: Confidence results

Variable	Coefficient	Jackknife SE	Covariance SE	t-value	t- probability	VIF	SSIncr	SSMarg
STRETCH-BEND	-0.280	0.0347587	0.0716155	-3.90487	0.000252111	1.341	0.121	0.117
OVALITY	0.496	0.0493592	0.0743351	6.67014	1.12582e-008	1.127	0.445	0.340
LIPOLE XCOMPONENT WM	0.0253	0.00264916	0.00401429	6.29834	4.64764e-008	1.528	0.0861	0.303
LIPOLE X COMP. SUB1	0.0560	0.00533854	0.022093	2.53392	0.0140529	1.861	0.0389	0.0491
LIPOLE Y COMP. WM	0.00533	0.000926729	0.00248417	2.14459	0.0362621	1.403	0.0555	0.0352
LIPOLE Y COMP. SUB1	0.0552	0.00496196	0.00924944	5.96968	1.61256e-007	1.185	0.290	0.272
BOND LIPOLE SUB1	0.0304	0.000539591	0.00833041	3.65096	0.000568856	2.474	0.140	0.102
DIPOLE/DIPOLE	-0.00416	9.77685e-005	0.00124056	-3.35136	0.00143235	1.275	0.0859	0.0859
CONSTANT	0.978	0.0797141						

The cross-validated correlation coefficient defines the goodness of prediction i.e. how reliable predicted values for untested compounds are likely to be, whereas the non-cross-validated conventional correlation coefficient indicates the goodness of fit of a QSAR model. The *F*-test value stands for the degree of statistical confidence. As evident from the table, a cross-validated correlation coefficient of 0.707 was obtained, using the leave-one-out cross-validation procedure.

Table 4: Statistical parameters obtained from the best model

No. of molecules in Training set	66
No. of molecules in Test set	14
Correlation co-efficient (r)	0.862
r^2 (Training Set)	0.743
r^2pred (Test Set)	0.6938
r^2 cv/ q^2	0.707
F value	18.668
s value	0.095
Predictive sum of square (training)	0.4885
Residual sum of square(training)	0.522
Predictive sum of square (test)	0.06478
Residual sum of square(test)	0.390067

Generally, the external predictive capability of a QSAR model is validated using test sets. A predictive correlation coefficient of 0.6938 was obtained from the study, indicating the usefulness of the developed QSAR in predicting activities of molecules not included during its development. Another way to evaluate the significance of the developed model is to test it for statistical stability. The standard error of estimate and a predictive residual sum of squares may be employed. Low values of the standard error of estimate (0.087) and of PRESS for the training (0.4885) and test sets (0.06478) further add to the statistical significance of the developed models. The experimental and calculated activity is shown in table 1 and 2. Fig.1 and 2 show plots of experimental *vs.* calculated percentage inhibition values for both the training and test set molecules respectively.

These two plots are important to observe graphically, the predictive capability of QSARs. The fact that the training set molecules are on or near the best-fit line, as shown in Fig. 2, further add to the usefulness of the developed QSAR. Table 5 shows the descriptors included in the final QSAR model and their statistical significance.

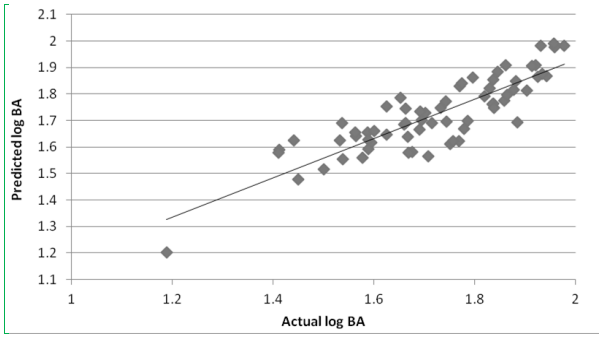


Figure 1: Correlation between actual and predicted log BA of training set

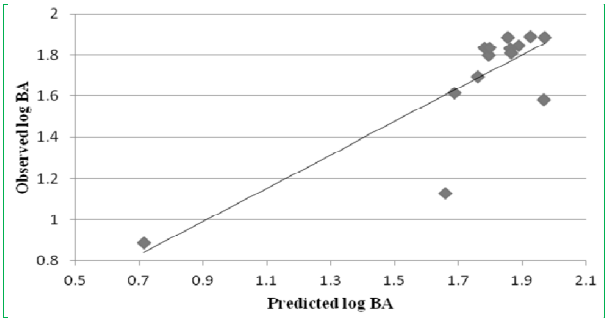


Figure 2: Correlation between actual and predicted log BA of test set

PRINCIPLE OF PARSIMONY (Occam's razor):

1. The number of compounds per variable in the equation should be at least five to six to avoid chance correlation. [At least n> 36, we have n= 66]

2. The equation should be rejected if the number of variables in the regression equation is unreasonably high (i.e. the model is very complex).

3. The standard deviation (standard error of estimate, s) should not be much greater than the mean error of the biological data. [Standard Error of Estimate = 0.087]. The mean error of log BA = 0.0198.

4. RMSE=0.078 for Training set. RMSE= 0.1864 for Test set.

RMSE summarizes the overall error of the model i.e. the precession of the QSAR and can thus be applied to predictions (i.e. RMSEP).[7]

Table 5: Descriptors included in the final QSAR model and their correlation with each other

	Log BA	Stretch-Bend	Dipole/Dipole	Ovality	Lipole X comp WM	Lipole X comp Sub.1	Lipole Y comp WM	Lipole Y sub 1	Bond Lipole Sub1.
Log BA	1	-0.0454	-0.319256	0.505269	0.250964	0.0767976	0.0202034	0.330975	0.114815
Stretch- Bend	-0.0454	1	0.358589	0.0244056	0.0924878	0.0523722	0.27964	-0.0945317	0.128317
Dipole/Dipole	-0.319256	0.358589	1	-0.0234866	0.247106	0.0752226	-0.0368692	-0.023277	-0.195789
Ovality	0.505269	0.0244056	-0.0234866	1	0.104807	-0.218894	-0.102133	-0.046386	0.168608
Lipole X comp WM	0.250964	0.0924878	0.247106	0.104807	1	0.254964	-0.14614	-0.246179	-0.488708
Lipole X comp Sub.1	0.0767976	0.0523722	0.0752226	-0.218894	0.254964	1	0.0576918	0.157284	-0.59117
Lipole Y comp WM	0.0202034	0.27964	-0.0368692	-0.102133	-0.14614	0.0576918	1	-0.245849	0.300144
Lipole Y sub 1	0.330975	-0.0945317	-0.023277	-0.046386	-0.246179	0.157284	-0.245849	1	-0.0462334
Bond Lipole Sub1.	0.114815	0.128317	-0.195789	0.168608	-0.488708	0.300144	0.300144	-0.0462334	1

CONCLUSION

The QSAR analysis using 80 glutamamide derivatives was successfully carried out to build a statistically significant model possessing a good correlative and predictive capability of inhibition of EAC cell. The 2D-QSAR model was validated by standard statistical means to check how it reproduces and explains the differences in the experimentally known activity data. Detailed QSAR model investigation revealed that the biological activity is explained by liable for both whole molecule and substituent1 along the X and Y-axis, which explains the lipophilic distribution of the inhibitors, except lipole Y comp WM, as the coefficient is insignificant. Ovality which explains as O= (A/4π) (3V/4π).$^{2/3}$ This property is an indicator of how close is the molecular geometry of a sphere, a cylinder or a disk. If O=1, it is a perfect sphere, if O>1.0 it is a cylinder and if O<1.0 it is closer to a disk. Although it is directly related to the molecular geometry (PM3) it also depends on the single-point level of calculation of the Wave function (*abinitio* HF/3-21G), since the density derived from it is used to compute the molecular volume employed in the ovality formula.[8] This provided an insight into how modulation of the steric bulkiness and polarity of the substituents could be useful to optimize the inhibitory effect and hence improve the observed biological activity. The electronic parameter (stretch-bend) Stretch-bend term represents the energy required to stretch the two bonds involved in a bond angle when that bond angle is severely compressed.

Stretch-bend cross terms are used when a coupling occurs between bond stretching and angle bending. For example, when an angle is compressed, the MM2 force field uses the Stretch-bend force constants to lengthen the bonds from the central atom in the angle to the other two atoms in the angle. It provides a clue about its effect on changing the values. Thermodynamic parameter (dipole-dipole) cannot explain much as the coefficient is statistically insignificant. This analysis could help rational design of potential drug candidates with enhanced inhibitor potency.

Acknowledgment: The authors gratefully acknowledge the University Grants Commission for their Minor Research Project Grant.

REFERENCES

1. Hansch C, Fujita T, Q-σ-π Analysis. A Method for the Correlation of Biological Activity and Chemical Structure, *J. Am. Chem. Soc.,* 86, 1964, 1616-1626.
2. Todeschini R, Consonni V, *Handbook of Molecular Descriptors*, Hard Cover Edition, 11, Wiley-VCH, Weinheim, Germany, 2000, 366.
3. Todeschini R, Program DRAGON; *www.disat.unimib.it/chm/Dragon.html*.
4. Unger S.H., Hansch C, A re-examination of adrenergic blocking activity of Beta-halo-beta-arylalkylamines, *J. Med. Chem.* 16, 1973, 745-749.
5. Sarvesh K, Singh S, Kumara S, Siddiqui Anees A, Paliwal S. K. QSAR studies of imidazo (1,5-α) quinoxalines amides, carbamates and ureas as potent GABA modulators, *Indian. J. of Chem.*, 49B, 2010, 554-560.
6. Lohary B.B, Gandhi N, Srivastav B. K, Lohary V, 3D QSAR studies of N-4-arylacryloylpiperazin-1-yl-phenyl-oxazolidinones: a novel class of antibacterial agents, *Bioorganic and Medicinacl Chemistry letters*, 16, 2006, 3817.
7. Aynur O, Aptula, Jeliazkova N.G, T. Schultz W. T, Mark T.D, Cornin, The Better predictive Model: High $q^2$for training set or Low root Mean Square Error of Prediction for The Test Set, *QSAR Comb. Sci.,* 24, 2005,387.
8. García M. V, Salazar N. H, Richa A. M, Robles J, Theoretical study of the experimental behavior of two homologous series of liquid crystals *ARKIVOC*, Part xi, 2003, 149-162.

****