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The Anticancer Activity of Some Novel 4-anilino quinazoline derivatives as tyrosine kinase (EGFR) inhibitor and the Quantitative Structure Activity Relationships

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Abstract

QSAR analysis of a set of previously synthesized 61 analogs of 4-anilino quinazoline derivatives as epidermal growth factor receptor (EGFR) protein tyrosine kinases (PTKs) are known for its role in cancer was performed by using the computer assisted multiple regression procedure. The QSAR study indicated the importance of electronic parameters, index of refraction, TWC and the topological parameter χ^2_v in contribution to the anticancer activity of 4-anilino quinazoline derivatives. Excellent statistically significant models were developed by this approach (r = 0.7384). The cross validated r^2 (q^2) which is an indication of the predictive capability of the model was also very good.

Key-Words: 4-anilino quinazoline derivatives, Anticancer Activity,QSAR

Introduction

Many of the tyrosine kinase enzymes are involved in cellular signaling path ways and regulate key cell functions such as proliferation, differentiation, anti-apoptotic signaling and neurite outgrowth. Unregulated activation of these enzymes, through mechanisms such as point mutations or over expression, can lead to a large percentage of clinical cancers [1-2].The importance of tyrosine kinase enzymes in health and disease is further underscored by the existence of aberrations in tyrosine kinase enzymes signaling occurring in inflammatory diseases and diabetes. Inhibitors of tyrosine kinase as a new kind of effective anticancer drug are important mediators of cellular signal transduction that affects growth factors and oncogenes on cell proliferation [3-4].

The development of tyrosine kinase inhibitors has therefore become an active area of research in pharmaceutical science. Epidermal growth factor receptor (EGFR) which plays a vital role as a regulator of cell growth is one of the intensely studied tyrosine kinase targets of inhibitors. EGFR is overexpressed in numerous tumors, including those derived from brain, lung, bladder, colon, breast, head and neck. EGFR hyper activation has also been implicated in other diseases including polycystic kidney disease, psoriasis and asthma [5-7]. Since the hyper activation of EGFR has been associated with these diseases, inhibitor of EGFR has potential therapeutic value and it has been extensively studied in the pharmaceutical industry.

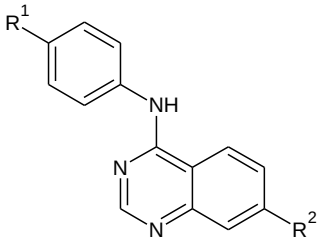

Fig.1. Structure of 4-(R^1- bromoaniline)-R^2-quniazolines

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One could not, however, confirm that the compounds designed would always possess good inhibitory activity to EGFR, while experimental assessments of inhibitory activity of these compounds are time-consuming and expensive. Consequently, it is of interest to develop a prediction method for biological activities before the synthesis. Quantitative structure activity relationship (QSAR) searches information relating chemical structure to biological and other activities by developing a QSAR model. Using such an approach one could predict the activities of newly designed compounds before a decision is being made whether these compounds should be really synthesized and tested.

Anilinoquinazolines are the most developed class of drugs that inhibit EGFR kinase intracellularly. Structure–activity relationship (SAR) studies reveal the nature of desirable substituents on the Anilinoquinazolines moiety. Electron withdrawing, lipophilic substituents at the 3-position of aniline are favorable with Cl and Br being optimal. Similarly, electron donating groups at the 6- and 7-positions of quinazoline are preferred [8-9].Bulky substituents appear to be tolerated at the 6- and 7-positions [10].QSAR studies by Hou *et. al.* have described the region around the 7-position as more electronegative than that near the 6-position [11].

Table 1. Substituent Structure of Quinazolines

No.	Substituent		No.	Substituent	
	R^1	R^2		R^1	R^2
1	H	H	31	3-I	6,7-Di-OMe
2^T	3-F	H	32	3-CF_3	6,7-Di-OMe
3	3-CI	H	33	3-Br	6-NHMe
4^T	3-Br	H	34	3-Br	6-NMe_2
5	3-I	H	35	3-Br	6-NHCOOMe
6^T	3-CF_3	H	36^T	3-Br	7-OH
7	H	6-OMe	37	3-Br	7-NHCOMe
8	3-Br	6-OMe	38	3-Br	7-NHMe
9^T	H	6-NH_2	39	3-Br	7-NHC_2H_5
10	3-CF_3	6-NH_2	40^T	3-Br	7-NMe_2
11	3-Br	6-NH_2	41	3-Br	6-7-Di-NH_2
12	H	6-NO_2	42	3-Br	6-NH_2,7-NHMe
13^T	3-Br	6-NO_2	43^T	3-Br	6-NH_2,7-NHMe
14	H	7-OMe	44	3-Br	6-NH_2,7-OMe
15	3-Br	7-OMe	45	3-Br	6-NH_2,7-CI
16	H	7-NH_2	46^T	3-Br	6-NO_2,7-NH_2
17	3-F	7-NH_2	47	3-Br	6-NO_2,7-NHMe
18^T	3-CI	7-NH_2	48	3-Br	6-NO_2,7-$NHMe_2$
19	3-Br	7-NH_2	49	3-Br	6-NO_2,7-NHCOMe
20	3-I	7-NH_2	50^T	3-Br	6-NO_2,7-Ome
21^T	3-CF_3	7-NH_2	51	3-Br	6-NO_2,7-CI
22	H	7-NO_2	52	3-Br	6,7-Di-OH
23	3-F	7-NO_2	53	3-Br	6,7-Di-OC_2H_5
24^T	3-CI	7-NO_2	54^T	3-Br	6,7-Di-OC_3H_7

25	3-Br	7-NO_2	55	3-Br	6,7-Di-OC_4H_9
26	3-I	7-NO2	56^T	3-Br	2-NH_2
27^T	H	6,7-Di-OMe	57	3-Br	5,6,7-Tri-Ome
28^T	3-F	6,7-Di-OMe	58	2-Br	6,7-Di-Ome
29	3-CI	6,7-Di-OMe	59	4-Br	6,7-Di-Ome
30	3-Br	6,7-Di-OMe	60^T	3,5-di-Br	6,7-Di-Ome
			61	3,5-di-Br	6,7-Di-Ome

With the above facts and in continuation of our research for newer anti-cancer agent in the present study, we reported QSAR studies on a series of EGFR kinase inhibitors to provide further insight into the key structural features required to design potential drug candidates of this class[12-13] . Here, we present our observations on the role of different substitution at the 4, 6- and 7-positions of quinazolines as EGFR inhibitor.

Material and Methods

COMPUTATIONAL METHODS

Chemical Data

A series of 61 molecules belonging to quinazoline derivatives as tyrosine kinase (EGFR) inhibitors were taken from the study by Bridges et al [14]. The 2D-QSAR models were generated using a training set of 42 molecules. The substituent structure of Quinazolines molecules are presented in Table 1. Predictive power of the resulting models was evaluated by a test set of 19 molecules with uniformly distributed biological activities. The observed selection of test set molecules was made by considering the fact that test set molecules represents a range of biological activity similar to the training set.

Data Set

All computational work was performed on Apple workstation (8-core processor) using E-Dragon 7.0 software on windows XP operating system . All the compounds were drawn in Chemsketch using fragment database and then subjected to energy minimization using batch energy minimization method. Conformational search were carried out by systemic conformational search method and all the compounds were aligned by template based method.

Biological Activities

The negative logarithm of the measured IC_{50} (μM) against tyrosine kinase (EGFR) as pIC_{50} [$pIC_{50} = -\log(IC_{50})$] was used as dependent variable, thus correlating the data linear to the free energy change. Since some compounds exhibited insignificant/no inhibition, such compounds were excluded from the present study**.** All the IC_{50} values had been obtained using human A431 carcinoma cell vesicles by immuno-affinity chromatography [14]. The IC_{50} values of reference compounds were checked to ensure that no difference occurred between different groups. The pIC_{50} values of the molecules under study spanned a wide range from 5 to 11.

Molecular Descriptors

Various 2D descriptors (a total of 208) like element counts, molecular weight, molecular refractivity, log P, topological index, Baumann alignment independent topological descriptors etc., were calculated using Dragon software**.** The preprocessing of the independent variables (i.e., descriptors) was done by removing invariable (constant column) and cross-correlated descriptors which resulted in total descriptors for MLR respectively to be used for QSAR analysis.

Selection of Training and Test Set

The dataset of 61 molecules was divided into training and test set by Sphere Exclusion (SE) method for MLR model with pIC_{50} activity field as dependent variable and various 2D descriptors calculated for the molecules as independent variables. This is done to test the internal stability and predictive ability of the QSAR models. Developed QSAR models were validated by the following procedure:

Internal Validation

Internal validation was carried out using leave-one-out (R^2, LOO) method. For calculating R^2, each molecule in the training set was eliminated once and the activity of the eliminated molecule was predicted by using the model developed by the remaining molecules. The R^2 was calculated using the equation which describes the internal stability of a model. where and are the actual and predicted activity of the i^{th} molecule in the training set, respectively, and y mean is the average activity of all molecules in the training set.

External Validation

For external validation, the activity of each molecule in the test set was predicted using the model developed by the training set. The $R^{'}$ value is calculated as follows. Where, and are the actual and predicted activity of the i^{th} molecule in the training set, respectively, and y

mean is the average activity of all molecules in the training set. Both summations are over all molecules in the test set. Thus, the R^2 value is indicative of the predictive power of the current model for external test set.

Randomization Test

To evaluate the statistical significance of the QSAR model for an actual dataset, one tail hypothesis testing was used [15-16]. The robustness of the models for training sets was examined by comparing these models to those derived for random datasets. Random sets were generated by rearranging the activities of the molecules in the training set. The statistical model was derived using various randomly rearranged activities (random sets) with the selected descriptors and the corresponding R^2 were calculated. The significance of the models hence obtained was derived based on a calculated Z score [17-20].

Where, h is the R^2 value calculated for the actual dataset, μ the average R^2, and σ is its standard deviation calculated for various iterations using models build by different random datasets. The randomization test suggests that all the developed models have a probability of less than 1% that the model is generated by chance.

QSAR by Multiple Linear Regression (MLR) Analysis

Multiple regressions is the standard method for multivariate data analysis. It is also called as ordinary least squares regression (OLS). This method of regression estimates the values of the regression coefficients by applying least squares curve fitting method. For getting reliable results, dataset having typically 5 times as many data points (molecules) as independent variables (descriptors) is required. The regression equation takes the form

$$Y = b_1*x_1 + b_2*x_2 + b_3*x_3 + c$$

where Y is the dependent variable, the 'b's are regression coefficients for corresponding 'x's (independent variable), 'c' is a regression constant or intercept. In the present study QSAR model was developed using multiple regression by forward-backward variable selection method with pIC50 activity field as dependent variable and topological and physicochemical descriptors as independent variable having cross-correlation limit of 1. Selection of test and training set was done by sphere exclusion method [21-24].

Table 2: Calculated Topological descriptors and Anticancer activity

S.No.	pIC_{50}	IR	ZM_2Per	MSD	SMTIV	GMTI	MAXDN	TWC	X^1v	X^2v	X^3v
1	6.463	1.721	375.71	4.325	3828	2471	0.832	11.885	5.452	3.73	2.579
2	7.251	1.699	429.26	4.516	4889	2836	1.946	11.974	5.551	3.875	2.63
3	7.638	1.723	429.26	4.516	4889	2836	0.974	11.974	5.929	4.311	2.865
4	7.568	1.737	429.26	4.516	4889	2836	0.848	11.974	6.344	4.79	3.123
5	7.096	1.772	429.26	4.516	4889	2836	0.831	11.974	6.63	5.12	3.301
6	6.238	1.63	564.59	5.096	8210	4183	5.62	12.224	6.179	4.443	2.995
7	7.259	1.688	433.51	4.688	5208	3225	0.893	12.047	5.975	4.096	2.879
8	7.522	1.704	487.06	4.875	6491	3658	0.91	12.123	6.867	5.156	3.423
9	6.113	1.767	403.72	4.47	4467	2808	0.964	11.996	5.651	3.99	2.696
10	6.241	1.667	592.6	5.242	9255	4660	5.643	12.304	6.379	4.702	3.112
11	9.107	1.779	457.27	4.66	5634	3205	0.973	12.076	6.544	5.05	3.24
12	5.301	1.745	614.53	4.847	7511	3646	2.625	12.128	5.258	3.495	2.255
13	6.045	1.759	673.32	5.033	9022	4115	2.628	12.199	6.162	4.419	2.699
14	6.92	1.688	433.52	4.828	5312	3289	0.878	12.043	5.975	4.096	2.88
15	8	1.704	487.07	5.017	6619	3730	0.893	12.119	6.867	5.156	3.424
16	7	1.767	403.73	4.547	4519	2840	0.966	11.993	5.651	3.99	2.697
17	8.698	1.743	457.28	4.739	5698	3241	1.965	12.073	5.751	4.134	2.748
18	9.602	1.766	457.28	4.739	5698	3241	0.993	12.073	6.129	4.571	2.983
19	10	1.779	457.28	4.739	5698	3241	0.973	12.073	6.544	5.05	3.241
20	9.455	1.814	457.28	4.739	5698	3241	0.966	12.073	6.829	5.38	3.419
21	8.481	1.667	592.61	5.32	9349	4708	5.639	12.302	6.379	4.702	3.113
22	4.92	1.745	614.53	5.033	7714	3742	2.627	12.123	5.258	3.495	2.255

23	5.214	1.724	673.32	5.224	9266	4223	2.673	12.193	5.369	3.626	2.302
24	6.091	1.746	673.32	5.224	9266	4223	2.641	12.193	5.747	4.004	2.491
25	6	1.759	673.32	5.224	9266	4223	2.629	12.193	6.162	4.419	2.699
26	6.267	1.792	673.32	5.224	9266	4223	2.624	12.193	6.448	4.705	2.842
27	7.537	1.663	495.21	5.008	6805	4091	1.019	12.228	6.504	4.438	3.177
28	8.42	1.647	548.76	5.199	8334	4600	1.984	12.292	6.603	4.582	3.228
29	9.508	1.667	548.76	5.199	8334	4600	1.043	12.292	6.981	5.018	3.463
30	10.602	1.679	548.76	5.199	8334	4600	1.026	12.292	7.396	5.498	3.721
31	9.05	1.707	548.76	5.199	8334	4600	1.02	12.292	7.682	5.828	3.899
32	9.619	1.598	684.09	5.784	12963	6427	5.665	12.479	7.231	5.15	3.593
33	8.397	1.758	470.16	4.875	6291	3658	0.87	12.123	7.005	5.255	3.505
34	7.057	1.727	487.47	5.033	6956	4115	0.859	12.199	7.373	5.869	3.716
35	7.92	1.739	574.88	5.608	10131	5385	2.192	12.222	7.571	5.622	3.648
36	8.327	1.77	469.66	4.739	5910	3241	1.473	12.073	6.479	4.975	3.201
37	7.397	1.748	529.63	5.582	8909	4888	1.777	12.19	7.459	5.686	3.537
38	8.154	1.758	470.17	5.017	6403	3730	0.865	12.119	7.005	5.255	3.506
39	7.92	1.735	478.87	5.34	7220	4307	0.86	12.144	7.566	5.536	3.598
40	7.958	1.727	487.48	5.224	7116	4223	0.858	12.193	7.373	5.869	3.717
41	9.92	1.822	487.69	4.836	6466	3618	1.149	12.19	6.749	5.272	3.421
42	9.161	1.796	500.82	5.072	7193	4119	1.003	12.24	7.21	5.48	3.657
43	6.798	1.762	518.37	5.249	7928	4624	0.968	12.318	7.578	6.096	3.846
44	8.42	1.741	518.18	5.072	7415	4119	1.114	12.24	7.073	5.385	3.567
45	8.187	1.778	514.17	4.836	6902	3618	1.176	12.19	7.027	5.571	3.662
46	7.275	1.798	706.99	5.131	10124	4552	2.786	12.321	6.386	4.643	2.861
47	7.167	1.776	735.21	5.294	11301	5085	2.718	12.37	6.61	4.754	2.973
48	5.698	1.745	767.03	5.418	12494	5622	2.776	12.446	6.833	4.978	3.084
49	7.552	1.766	800.41	5.686	14383	6355	3.028	12.438	7.064	5.059	3.074
50	7.823	1.725	747.38	5.294	11423	5085	2.75	12.37	6.571	4.725	2.949
51	7.602	1.758	721.09	5.131	10358	4552	2.668	12.321	6.729	4.986	3.109
52	9.769	1.803	513.41	4.836	6886	3618	1.871	12.19	6.619	5.131	3.312
53	11.211	1.652	571.14	5.604	10078	5814	0.973	12.343	8.571	5.955	3.881
54	9.769	1.631	584.38	6.048	12146	7292	0.945	12.373	9.571	6.786	4.205
55	6.978	1.615	595.98	6.529	14578	9066	0.927	12.395	10.571	7.493	4.792
56	6.334	1.779	464.21	4.591	5562	3169	1.406	12.091	6.564	4.999	3.201
57	9.245	1.658	614.21	5.21	9998	5422	1.167	12.509	7.931	5.813	4.01
58	6.892	1.679	552.08	5.109	8157	4532	1.028	12.315	7.402	5.406	3.959
59	9.017	1.679	548.47	5.3	8512	4668	1.025	12.285	7.396	5.494	3.776
60	10.142	1.693	602.65	5.349	9925	5121	1.034	12.362	8.289	6.561	4.182
61	6.946	1.693	602.65	5.349	9925	5121	1.034	12.362	8.289	6.561	4.182

Results and Discussion

After 2D QSAR study by Multiple Linear Regression method using forward-backward stepwise variable selection method, the final QSAR equation developed QSAR/QSPR models was as follows. The highest correlation coefficient ($r \geq 0.8$) between the descriptors as illustrated in Table 3.

Table 3: Correlation matrix between different descriptors and anticancer activity

	pIC_{50}	IR	ZM_2Per	MSD	SMTIV	MAXDN	TWC	X^1v	X^2v	X^3v
pIC_{50}	1.0000									
IR	-0.1196	1.0000								
ZM_2Per	-0.2043	-0.1021	1.0000							
MSD	0.1202	-0.4865	0.6417	1.0000						
SMTIV	0.0071	-0.3617	0.8782	0.9044	1.0000					
MAXDN	-0.2820	-0.2277	0.5757	0.2783	0.4569	1.0000				
TWC	0.2040	-0.4049	0.7720	0.8139	0.8934	0.3605	1.0000			
X^1v	0.4551	-0.3916	0.1532	0.7323	0.5437	-0.2591	0.5986	1.0000		
X^2v	0.4927	-0.2256	0.0675	0.6023	0.4220	-0.3085	0.5266	0.9598	1.0000	
X^3v	**0.5514**	-0.3562	-0.0488	0.5399	0.3321	-0.3442	0.5008	0.9392	0.9645	1.0000

With reference to Table 3 the selected descriptors are used for biparamatric QSAR model no.1 development which show the importance of topological descriptor total walk count (TWC) which is directly proportional with the anticancer activity while the another topological descriptors second Zagreb index by perturbation vertex degrees (ZM_2per) is negatively correlated with the anticancer activity. The under given model enocoded the information about the structural changes which can be applied over the parent structure. The QSAR model no. 1 reveals the relationship between the Biparametric QSAR model No.1 is given below;

pIC_{50}=-95.8135+ 9.0563TWC-1.2582E-02ZM_2per

Eq….. 1

From QSAR model Equation no. 1 the low statistical results indicates needs for the development of Triparametic or more multiparamteric QSAR models follow by rule of thumb. The QSAR model no.2 has significant importance in which TWC and X^1V has positive contribution with the anticancer activity while the physicochemical descriptor index of refraction show inverse contribution with anticancer activity. The statistical descriptors are given in Table no.4 (Model No.2).

pIC_{50}= -57.4706+ 5.6623TWC+ 2.57981X^1_V-3.47394E-02IR Eq……2

The QSAR model no. 3 show their significant statistical importance with quadratic parametric model in which TWC and X^1v are directly proportional with the anticancer activity while IR and MAXDN are inversely proportional with the anticancer activity.

pIC_{50}=-103.0443+9.8061TWC+ 2.4465X^1_V-4.0142E-02IR-0.4308MAXDN

Eq……. 3

The above described all models are not statistically excellent indicates the deletion of outliers compound whose activity are not uniform and After deleting Comp No.6,10,18,19,43,56,58 and 61 resulting the development of high statistically significant qsar model no.4 indicates that the TWC play a major role in the anticancer activity of 4-(R^1- bromoaniline)-R^2-quniazolines derivatives and index of refraction affect very low.

pIC_{50}=-138.4808+ 12.9285TWC+ 3.3158X^1_V-5.4181E-02IR-0.2908MAXDN

Eq……4

The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance. Statistical data is shown in Table 4.The observed and predicted pIC_{50} along with residual values are shown in Table 6. The plot of observed vs. predicted activity is shown in Fig. (2). From the plot it can be seen that MLR model is able to predict the activity of training set quite well (all points are close to regression line) as well as external.

Table 4: Validated Statistical and Cross Validated Descriptors of Developed QSAR/QSPR models

Model	n	Intercept	R^2	F-Ratio	PRESS	R^2_{CV}	R^2_{ADJ}
1	61	-95.8100	0.36	16.726	85.1738	0.3038	0.3439
2	61	-57.4707	0.41	12.723	89.2137	0.2708	0.3695
3	61	-103.0444	0.47	12.490	80.5212	0.3419	0.4337
4	**54**	**-138.4808**	**0.73**	**33.543**	**36.5201**	**0.6502**	**0.7146**

The above study leads to the development of statistically significant QSAR model, which allows understanding of the molecular properties/features that play an important role in governing the variation in the activities. In addition, this QSAR study allowed investigating influence of very simple and easy-to-compute descriptors in determining biological activities, which could shed light on the key factors that may aid in design of novel potent molecules.

Table-5: Results of Regression Analysis

No.	Parameters Used	Ai (1,…..3)	Intercept	F-Ratio	R^2	AR^2
1	TWC ZM2R	9.0563 -1.2582E-02	-95.8135	16.726	0.36	0.3439
2	TWC X^2_V IR	5.6623 2.5798 3.4739E-02	-57.4706	12.723	0.41	0.3695
3	TWC X^2_V IR MAXDN	9.8061 2.4465 -4.0142E-02 -0.4308	-103.0443	12.490	0.47	0.4337
4	TWC X^2_V IR MAXDN	12.9285 3.3158 -5.4181E-02 -0.2908	-138.4808	33.543	0.73	0.7146

Table-6: Actual and Predicted anticancer activity of 4-(R^1- bromoaniline)-R^2-quniazolines

Com. No.	Actual pIC_{50}	Predicted pIC_{50}	Residual
1	6.463	6.316	0.147
2	7.251	7.087	0.164
3	7.638	7.062	0.576
4	7.568	7.684	-0.116
5	7.096	7.277	-0.181
7	7.259	7.055	0.204
8	7.522	8.254	-0.732
9	6.113	6.975	-0.862
11	9.107	8.232	0.875
12	5.301	5.286	0.015
13	6.045	6.465	-0.420
14	6.920	7.008	-0.088
15	8.000	8.208	-0.208

16	7.000	6.936	0.064
17	8.698	7.621	1.077
20	9.455	7.780	1.675
21	8.481	8.886	-0.405
22	4.920	5.221	-0.301
23	5.214	6.096	-0.882
24	6.091	5.804	0.287
25	6.000	6.387	-0.387
26	6.267	5.977	0.290
27	7.537	8.046	-0.509
28	8.42.	8.531	-0.111
29	9.508	8.503	1.005
30	10.602	9.093	1.509
31	9.050	8.683	0.367
32	9.619	9.251	0.368
33	8.397	8.604	-0.207
34	7.057	8.475	-1.418
35	7.920	7.882	0.038
36	8.327	8.417	-0.090
37	7.397	8.285	-0.888
38	8.154	8.554	-0.400
39	7.920	8.583	-0.663
40	7.958	8.398	-0.440
41	9.920	8.931	0.989
42	9.161	9.360	-0.199
44	8.420	8.993	-0.573
45	8.187	9.303	-1.116
46	7.275	7.341	-0.066
47	7.167	6.943	0.224
48	5.698	6.313	-0.615
49	7.552	6.810	0.742
50	7.823	6.929	0.894
51	7.602	7.971	-0.369
52	9.769	9.465	0.304
53	11.211	9.351	1.860
54	9.769	8.750	1.019
55	6.978	8.048	-1.070
57	9.245	10.559	-1.314
59	9.017	9.003	0.014
60	10.142	10.22	-0.078

The values obtained from the descriptors calculations explain the structural parameters and the possible interaction with the binding site of enzyme. Quinazoline act primarily by binding to ATP binding site of protein kinase. Though ATP binding site is highly conserved among the protein kinase, architecture in the regions proximal to ATP binding site does afford key diversity. The binding interactions of quinazolines with nucleotide are of lipophilic/van der Waals nature.

Nitrogen atoms of aniline group and quinazoline ring are involved in hydrogen bond formation with the hinge region of protein kinase. Hydrophobic channel

used to gain binding site of protein kinase is important in improving the selectivity of inhibitors. Methoxy group is going to interact with sugar region. The backbone carbonyl of the residue corresponding to valine serves as a hydrogen bond acceptor for inhibitor binding.

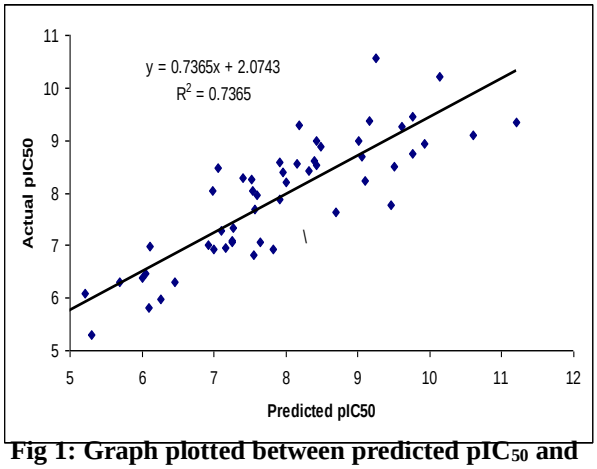

Fig 1: Graph plotted between predicted pIC_{50} and actual pIC_{50}

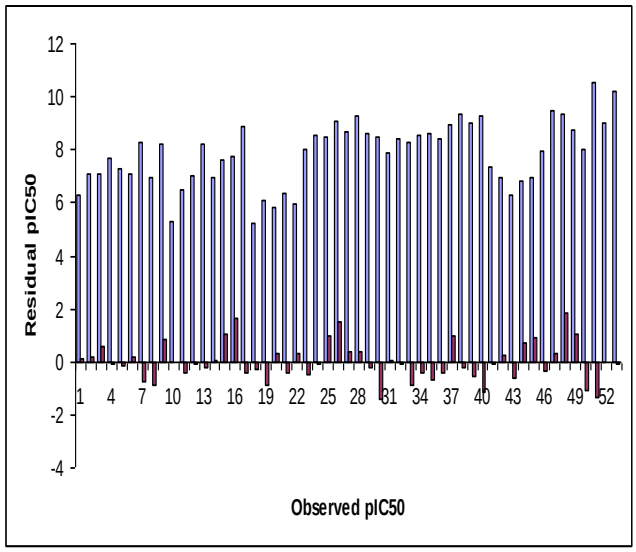

Fig 2: Graph between observed pIC_{50} and Residuals of developed QSAR model

Conclusion

Descriptor values obtained helps us to understand the structural features required by ATP binding site of EGFR tyrosine kinase. The QSAR results obtained are in agreement with the observed SAR of quinazoline studied. Hence, the model proposed in this work is useful in describing QSAR of quinazoline derivatives as EGFR tyrosine kinase inhibitor and can be employed to design new derivatives of quinazoline with specific inhibitory activity.

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