Quantitative Structure Activity Relationship Study of New 2- Aryl Carbonyl -3-Trifluoromethylquinoxaline 1, 4-Di-*N*- Oxide Derivatives and Their Reduced Analogues

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Abstract

A set of thirty three quinoxaline derivatives with cytotoxic activities against nine type of tumoral subgroups when subjected to 2D Quantitative Structure Activity Relationship (QSAR) analysis using various combination of descriptors through multiple linear regression led to three statistically significant models for leukemia, melanoma and ovarian cancer cells (all with r^2>0.7, F>> tabulated value, and chance correlation <0.001) having acceptable statistical quality and predictive potential as indicated by the value of cross validated squared coefficient (q^2>0.58). Alignment independent descriptors (T_ C_C_6, T_T_O_4, T_T_O_6, and T_2_O_4), and Polar Surface Area (Polar Surface Area excluding P and S) were found to have significant correlation with biological activity.

Key words: *2D QSAR, Quinoxaline derivatives, anticancer.*

Introduction

The effectiveness of cancer chemotherapy is mostly limited due to two major problems which are still to be overcome, the lack of selectivity of anticancer agents and occurrence of intrinsic or acquired resistance leading to significant side effects and sometimes, failure of treatment. [1]Quinoxaline derivatives are a class of substances possessing a broad spectrum of pharmacological activities including anticancer [2]. As an attempt to find more selective and potent anticancer agents, a series of thirty three quinoxaline derivatives (Fig.1) having good activities against leukemia, nonsmall lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancers have been subjected to 2D QSAR study.

The descriptors used in deriving the QSAR models mentioned herein included both, physiological and alignment independent topological descriptors, the latter being calculated by the software as described by Knut Baumann[3]. Alignment independent descriptors are the molecular descriptors based upon a count statistic of the topological distance matrix where encoding of molecule is done by computing many selective count statistics (histograms) reflecting the distribution of different atom types and bond types in the molecule. The descriptors also incorporate geometric features of molecules by weighting the topological distance counts with the geometric distance. It is invariant to both translation and rotation. As a result, it does not require the alignment of the structures under study. The QSAR models developed using these descriptors performed equally well or better than Comparative molecular field analysis (CoMFA) [4] and the EVA[5,6] descriptor. Compared to the latter two methods, it is computationally easier.

Materials and Methods

All the computational work was performed on Compaq PC having Pentium IV processor and windows XP operating system, using the software namely: Molecular Design Suite supplied by the

VLifeSciences, Pune (VLife MDS) [7]. The growth inhibitory data of quinoxaline derivatives (Table 1) against nine types of tumor cells were collected from reported work of Beatriz Solano et.al. [8]. All the biological activity data (Gi_{50} inμM) were converted to –log Gi_{50} (Table 2A and 2B)to reduce skew ness of data set. The thirty three compounds were manually divided into training set (twenty three compounds) and test set (ten compounds) according to Alexander Golbraikhet. al.[9] who recommend that training and test sets must satisfy the following criteria (i)representative points of the test set must be close of those to the training set, (ii)representative points of the training set must be close to the representative points of the test set, and (iii)training set must be diverse. This approach resulted in selection of compound 4, 5,6,7,10,15,27,28,29 and 30 as test set, and remaining twenty three compounds as training set. The unicolumn statistics of test and training sets (Table 3) further reflected the right selection of test and training sets as maximum of training set was more than maximum of test set; and minimum of training set was less than the minimum of test set. This showed that the test set was interpolative i.e. derived within the minimum – maximum range of the training set. The average and standard deviation of the training and test set provided insight to the relative difference of mean and point density distribution (along mean) of the two sets.

The structures of quinoxaline derivatives were constructed using the 2D draw application and converted to 3D structures by sending them to MDS. Energy minimization and geometry optimization was conducted using Merck Molecular Force Field (MMFF) method with Root Mean Square (RMS) gradient set to 0.01 Kcal/mol Å and iteration limit to 10000. The basis of energy minimization is that the drug binds to effectors/receptors in the most stable form i.e. minimum energy form. All the 2D descriptor like heat of formation, dipole moment, local charges, different alignment independent topological descriptors, elemental count including bromine count, fluorine count, path count, constitutional descriptors, chemical descriptors like molar volume, molecular surface area,

hydrophobicity, hydrogen acceptor count, hydration energy and molecular polarizability were calculated for these geometrically optimized structures. The invariable descriptors (the descriptors that are constant for all the molecules) were removed, as they do not contribute to QSAR.

The whole thirty three compounds for all the activities except prostate and thirty two compounds (as compound 17 has no activity against prostate cancer) for prostate were subjected to regression analysis using MLR as model building method coupled with stepwise variable selection. QSAR equations were generated by using – 1og Gi_{50} values as dependent variable and various parameter values as independent variables. Regression analysis was carried out for cytotoxic activity and the best model cross-validated. Cross correlation limit was set as 0.5, number of variable in final equation as 5, and term selection criteria as r^2, F-test 'in' as 4 and F-test 'out' as 3.99. Variance cut off was set to 0 and scaling as auto scaling, number of random iteration was set to 10. Following statistical parameters were considered to compare the generated QSAR models: correlation coefficient (r), squared correlation coefficient (r^2), predicted r^2 (pred_ r^2), and Fischer's value (F). In order to validate the generated QSAR models Leave One Out (LOO) method was used indicated as value of q^2 (cross-validated explained variance) which is a measure of internal predictive ability of the model. The method resulted in three statistically significant models (Model 1, 2, and 3) considering the term selection criteria as r^2 (Table 4). The statistical significance of these models was further supported by the 'fitness plots' obtained for each model which is a plot of observed Vs predicted activity of training and test set compounds and provides an idea about how well the model was trained and how well it predicts the activity of external test set (Fig.2). The nearness of observed to predicted activity presented in Table 4 also aids to this fact.

The contribution charts for all the significant models are presented in Fig. 3 which gives the percentage contribution of the descriptors used in deriving the model.

Results and Discussion

The 2D QSAR study of thirty three compounds (divided into ten test and twenty three training) for different cytotoxic activities through MLR analysis using VLife MDS resulted in following statistically significant models, considering the term selection criteria as r^2.

The statistically significant model (Model 1) with coefficient of determination (r^2) = 0.7042 (which corresponds to value of r=0.84) was considered as a *model for leukemia*. The model showed an internal predictive power (q^2=0.6002) of 60% and predictivity for external test set (pred_r^2 =0.1832) about 20%. The overall statistical significance level was found to be better than 99.9% as it exceeded the tabulated $F_{1, 21\alpha 0.001}$= 4.35.

Model 1

Log10 (Gi_50) =+ 0.0757 PolarSurfaceAreaExcludingPandS+ 0.1609 T_C_C_6 - 4.1679

n = 23; Degree of freedom = 20; r2 = 0.7042; q2 = 0.6002; F test = 23.8058

r2 se = 0.5611 ;q2 se = 0.6523 ;pred_r2 = 0.1832 ;pred_r2se = 1.0276 .

The developed MLR model reveals that the descriptor Polar surface area excluding P and S (i.e. Phosphorus and sulfur) plays most important role (~70%) in determining cytotoxic activity. This suggests that substituents like –OH, -NH_2, -NO_2 would increase the activity. The next important descriptor T_C_C_6, which is also directly proportional to the activity, implies the significance of number of carbon atoms separated from any carbon atom by 6 bond distance in a molecule. The descriptor explains the importance of primary, secondary or tertiary alkyl substitution at position 6 or 7.

In case of cytotoxic activity against melanoma the method resulted in statistically significant model, model 2 (*model for melanoma cancer*) having the value of coefficient of determination r^2=0.73 which corresponds to a value of r = 0.85. Also, the model had internal predictive power of about 60% and external predictivity of 62%. The overall statistical significance level was found to be better than 99.9% as it exceeded the tabulated $F_{1,20\alpha0.001}$= 4.35.

Model 2

Log10 (Gi_50)= -0.2120 T_T_O_4+ 0.1115 T_T_O_6+ 3.0049

n = 23; Degree of freedom = 20; r2 = 0.7314; q2 = 0.5886; F test = 27.2249

r2 se = 0.3868 ;q2 se = 0.4787 ;pred_r2 = 0.6236 ;pred_r2se = 0.4428

This model includes descriptors T_T_O_4 (~66%) contributing negatively, and T_T_O_6 (~40%), contributing positively to the biological activity. The descriptors indicate the importance of no. of any atoms attached to oxygen atom by 4 bonds and 6 bonds distance in a molecule respectively. Thus compounds with, phenyl/naphthyl groups at position A will be more active against melanoma cancer than furyl or thienyl ring.

The third statistically significant model, model 3 *(model for ovarian cancer)* explained 76% of variance (q2 = 0.7617) having an equivalent value of r = 0.87. The internal and external predictivity of the model was 67% (q2=0.6759) and 64% (pred_r2=0.6462) respectively. This model also explained statistical significance better than 99.9% as the obtained F value exceeded the tabulated $F_{1,\ 20\alpha0.001}$= 4.35.

Model 3

Log10 (Gi_50) =+ 0.0427 PolarSurfaceAreaExcludingPandS -0.1264 T_2_O_4+ 0.7206

n = 23; Degree of freedom = 20; r2 = 0.7617; q2 = 0.6759; F test = 31.9605

r2 se = 0.3582 ;q2 se = 0.4177 ;pred_r2 = 0.6462 ;pred_r2se = 0.4548

Here, polar surface area excluding P and S (i.e. phosphorous and sulphur) which has major (~70%) contribution in the positive direction for the biological activity. The later descriptor was T_2_O_4 which was a minor (~30%) contributor for biological activity. The descriptor means the count of number of double bonded atoms separated from oxygen by 4 bonds in a molecule, which is having a negative impact on the biological activity.

Conclusion

Three statistically sound predictive QSAR models, providing several important physico-chemical and topological properties crucial for growth inhibitory activity against various tumoral sub groups amongst quinoxaline derivatives have been reported. Alignment independent descriptors like T_T_O_6 and T_C_C_6 showed a positive correlation, while descriptors T_T_O_4 and T_2_O_4 showed a negative correlation with observed growth inhibitory activity against the said tumor cells. Physicochemical descriptor PolarSurfaceAreaExcludingPandS plays a positive role in determining the activity. The results suggested that the growth inhibitory activity was highly dependent on molecular size and polarity of the quinoxaline derivatives. The derived models and conclusion derived therein could be used in designing more potent anticancer compounds.

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Table1: Structures of 2 Arylcarbonyl 3-trifluromethylquinoxaline 1, 4 –Di– *N*– oxide derivatives and their reduced analogs

Compound	Ra	Rb	A
1	H	F	phenyl
2	H	CF3	phenyl
3	CF3	H	phenyl
4	F	F	naphthyl
5	Cl	Cl	naphthyl
6	H	F	naphthyl
7	H	Cl	naphthyl
8	H	CF3	naphthyl
9	CF3	H	naphthyl
10	H	H	thienyl
11	CH3	CH3	thienyl
12	F	F	thienyl
13	Cl	Cl	thienyl
14	H	CH3	thienyl
15	H	OCH3	thienyl
16	H	F	thienyl
17	H	Cl	thienyl

18	H	CF3	thienyl
19	CF3	H	thienyl
20	H	H	furyl
21	F	F	furyl
22	Cl	Cl	furyl
23	H	CH3	furyl
24	H	OCH3	furyl
25	H	F	furyl
26	H	Cl	furyl
27	H	CF3	furyl
28	CF3	H	Furyl

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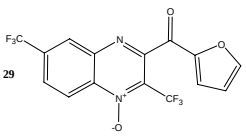

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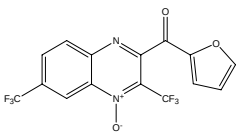

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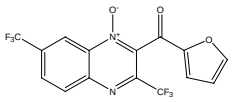

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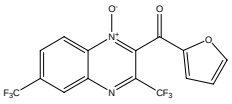

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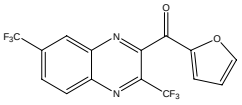


Table 2A Cytotoxic activities (mean Gi_{50} µM Inhibition Cell Growth and pGi_{50}) against tumoral subgroup cell lines of Quinoxaline derivatives

Comp	Leukemia		Nonsmall lung		Colon		CNS		Melanoma	
	Gi_{50}	pGi_{50}	Gi_{50}	pGi_{50}	Gi_{50}	pGi_{50}	Gi_{50}	pGi_{50}	Gi_{50}	pGi_{50}
1	0.23	-0.638	0.80	-0.097	0.54	-0.267	1.45	0.161	0.95	-0.022
2	0.24	-0.619	0.64	-0.194	0.46	-0.337	0.69	-0.161	1.13	0.053
3	0.77	-0.113	1.66	0.220	1.04	0.017	1.71	0.233	1.23	0.089
4	0.77	-0.113	3.47	0.540	1.71	0.233	2.51	0.399	2.50	0.397
5	1.58	0.198	1.70	0.100	1.55	0.190	1.63	0.212	1.57	0.195
6	0.44	-0.356	1.54	0.187	0.74	-0.130	1.61	0.206	1.12	0.049
7	0.65	-0.187	1.51	0.178	1.29	0.110	1.47	0.167	1.23	0.089
8	0.26	-0.585	1.42	0.152	0.66	-0.180	0.95	-0.022	0.97	-0.013
9	1.20	0.079	1.78	0.250	1.73	0.238	1.72	0.235	1.48	0.170
10	13.93	1.144	0.35	-0.456	0.83	-0.081	1.45	0.161	1.39	0.143
11	2.71	0.433	2.81	0.448	5.31	0.725	3.05	0.484	3.99	0.600
12	0.05	-1.301	0.83	-0.081	0.27	-0.568	0.44	-0.356	0.39	-0.408
13	0.02	-1.699	2.04	0.309	0.59	-0.229	0.67	-0.174	0.94	-0.026
14	0.49	-0.309	0.56	-0.252	0.88	-0.055	0.75	-0.125	0.90	-0.045
15	4.43	0.646	3.93	0.594	7.08	0.850	6.24	0.795	5.89	0.770
16	0.27	-0.568	1.68	0.225	0.92	-	1.63	0.212	1.51	0.178

						0.036				
17	0.07	-1.155	0.07	-1.154	0.04	-1.397	0.09	-1.045	0.12	-0.920
18	0.20	-0.699	0.45	-0.346	0.38	-0.420	0.48	-0.318	0.90	-0.045
19	0.03	-1.523	0.30	-0.522	0.15	-0.824	0.18	-0.744	0.33	-0.481
20	0.07	-1.155	0.35	-0.456	0.51	-0.292	0.40	-0.398	0.67	-0.173
21	0.43	-0.366	0.73	-0.136	0.19	-0.721	0.37	-0.431	0.56	-0.251
22	0.27	-0.568	0.28	-0.553	0.50	-0.301	0.79	-0.102	1.57	60.195
23	0.26	-0.585	0.47	-0.328	1.17	0.068	0.74	-0.130	0.88	-0.055
24	3.96	0.597	3.49	0.542	2.51	0.399	3.20	0.505	3.03	0.481
25	0.30	-0.522	3.13	0.495	1.06	0.025	2.35	0.371	1.56	0.193
26	0.19	-0.721	0.36	-0.443	0.21	-0.677	0.77	-0.113	0.49	-0.309
27	0.21	-0.677	0.76	-0.1191	0.57	-0.244	0.91	-0.040	1.11	0.045
28	0.13	-0.886	0.48	-0.318	0.28	-0.552	0.81	-0.091	0.86	-0.065
29	51.09	1.708	48.14	1.682	41.41	1.617	45.53	1.658	42.90	1.632
30	48.42	1.685	41.93	1.622	75.11	1.875	35.48	1.549	46.11	1.663
31	88.10	1.945	39.41	1.595	49.79	1.697	25.31	1.403	31.52	1.498

32	43.65	1.639	47.74	1.679	85.39	1.931	24.45	1.388	80.58	1.906
33	53.95	1.732	81.52	1.911	100.0	2.000	75.86	1.880	100.0	2.000

Comp.	Ovarian		Renal		Prostate		Breast	
	Gi_{50}	pGi_{50}	Gi_{50}	pGi_{50}	Gi_{50}	pGi_{50}	Gi_{50}	pGi_{50}
1	1.34	0.127	1.14	0.056	0.53	-0.275	0.73	-0.136
2	0.58	-0.236	0.33	-0.481	0.27	-0.568	0.54	-0.267
3	1.18	0.071	1.47	0.167	1.32	0.120	1.41	0.149
4	3.80	0.579	2.18	0.338	1.46	0.164	2.36	0.372
5	1.51	0.178	1.64	0.214	1.55	0.190	1.62	0.209
6	1.20	0.079	1.48	0.170	1.62	0.209	1.70	0.230
7	1.20	0.079	1.38	0.139	1.48	0.170	1.15	0.060
8	0.47	-0.327	0.58	-0.236	0.57	-0.244	0.99	-0.004
9	1.69	0.227	1.55	0.190	1.51	0.178	1.67	0.222
10	0.75	-0.124	0.48	-0.318	0.40	-0.397	0.85	-0.070
11	2.34	0.369	4.62	0.664	3.89	0.589	3.08	0.488
12	0.53	-0.275	0.50	-0.301	0.51	-0.292	0.41	-0.387
13	1.16	0.064	1.60	0.204	0.79	-0.102	0.79	-0.102
14	0.27	-0.568	0.25	-0.602	0.89	-0.050	0.56	-0.251
15	4.99	0.698	5.11	0.708	2.48	0.394	4.92	0.691
16	1.17	0.068	1.65	0.206	1.51	0.178	1.19	0.075

17	0.16	-0.795	0.03	-1.522	-	-	0.08	-1.096
18	0.43	-0.366	0.31	-0.508	0.20	-0.698	0.50	-0.301
19	0.20	-0.698	0.24	-0.619	0.15	-0.823	0.18	-0.744
20	1.45	0.161	0.33	-0.481	0.20	-0.698	0.76	-0.119
21	0.39	-0.408	0.36	-0.443	0.42	-0.376	0.20	-0.698
22	1.65	0.217	0.31	-0.508	0.33	-0.481	1.38	0.139
23	0.85	-0.070	0.58	-0.236	0.24	-0.619	0.66	-0.180
24	2.51	0.399	1.74	0.240	3.16	0.499	2.88	0.459
25	2.03	0.307	2.41	0.382	2.60	0.414	1.33	0.123
26	0.56	-0.251	0.20	-0.698	0.11	-0.958	0.28	-0.552
27	0.72	-0.142	0.43	-0.366	0.42	-0.376	0.57	-0.244
28	0.65	-0.187	0.49	-0.309	0.19	-0.721	0.48	-0.318
29	42.49	1.628	60.60	1.782	51.88	1.715	32.04	1.505
30	42.99	1.633	49.69	1.696	35.08	1.545	59.11	1.771
31	29.29	1.466	28.59	1.456	38.46	1.585	34.33	1.535
32	40.43	1.606	34.57	1.538	44.67	1.650	38.52	1.585
33	90.85	1.958	100.00	2.000	100.00	2.000	84.00	1.924

(-) indicates absence of biological activity

Table 3 Unicolumn Statistics of Training and Test sets for different Cytotoxic activities

Activity against:	Training / Test set	Average Max.	Max.	Min.	Std. Dev.	Sum
1. Leukemia	Training	-0.2915	1.9450	-1.6990	0.9836	-6.7042
	test	0.3161	1.7083	-0.8861	0.9395	3.1614
2. Melanoma	Training	0.2005	2.0000	-0.9208	0.7161	4.6123
	Test	0.4922	1.6638	-0.0655	0.6530	4.9222
3. Ovarian	Training	0.1324	1.9583	-0.7959	0.6995	3.0450
	Test	0.4422	1.6334	-0.1871	0.6914	4.4222

Table 4 Observed and predicted activities of training and test set compounds in statistically significant models

Comp.No.	Model 1		Model 2		Model 3	
	Obs.	Pred.	Obs.	Pred.	Obs.	Pred.
1	-1.699	-1.2668	-0.9208	-0.2427	-0.7959	-0.1932
2	-1.5229	-0.945	-0.4815	+0.0919	-0.699	-0.1932
3	-1.301	-1.2668	-0.4089	-0.1312	-0.5686	-0.1932
8	-1.1549	-0.2722	-0.3098	+0.0029	-0.4089	+1.1154
9	-1.1549	-1.2668	-0.2518	+0.114	-0.3665	-0.1932
11	-0.7212	-0.2722	-0.1739	-0.1091	-0.3279	-0.1932
12	-0.699	-0.945	-0.0555	+0.0024	-0.2757	-0.1932
13	-0.6383	-0.7841	-0.0458	+0.0919	-0.2518	+0.1154
14	-0.6198	-0.4622	-0.0458	-0.2427	-0.2366	-0.1932
16	-0.585	+0.0496	-0.0269	-0.1312	-0.0706	+0.1154
17	-0.585	+0.1814	-0.0223	-0.2427	+0.0645	-0.1932
18	-0.5686	-0.2722	-0.0132	+0.3149	+0.0682	-0.1932
19	-0.5686	-1.2668	+0.0531	+0.0919	+0.0719	-0.1932
20	-0.5229	-0.2722	+0.0899	+0.0919	+0.1271	-0.1932
21	-0.3665	-0.2722	+0.1703	+0.3149	+0.1614	+0.1154
22	-0.3098	-0.945	+0.179	-0.2427	+0.2175	+0.1154
23	-0.1135	-0.4622	+0.1931	+0.0024	+0.2279	-0.1932
24	+0.792	+0.1814	+0.1959	+0.114	+0.3075	+0.1154
25	+0.433	-0.6231	+0.4814	+0.0245	+0.3692	-0.1932
26	+0.5977	+0.5873	+0.601	-0.1312	+0.3997	+0.2569

31	+1.64	+0.9851	+1.4986	+1.375	+1.4667	+1.149
32	+1.732	+1.9206	+1.9062	+1.152	+1.6067	+1.149
33	+1.945	+0.9851	+2	+2.3015	+1.9583	+2.309
4*	-0.8861	+0.0496	-0.0655	+0.337	-0.1871	+0.1154
5*	-0.6778	+0.0496	+0.0453	+0.337	-0.1427	+0.1154
6*	-0.3565	-0.1404	+0.0492	-0.0196	-0.1249	-0.1932
7*	-0.1871	-0.1404	+0.0899	-0.0196	+0.0792	-0.1932
10*	-0.1135	-0.1404	+0.143	-0.3542	+0.0792	-0.1932
15*	+0.1987	-0.1404	+0.1959	+0.8919	+0.179	-0.1932
27*	+0.6464	-0.4073	+0.3979	+0.0919	+0.5798	-0.1932
28*	+1.144	-1.2668	+0.7701	-0.2206	+0.6981	-0.1932
29*	+1.685	+0.9851	+1.6325	+1.2635	+1.6283	+1.2754
30*	+1.7083	+0.9851	+1.6638	+1.4866	+1.6334	+1.2754

*test set compounds

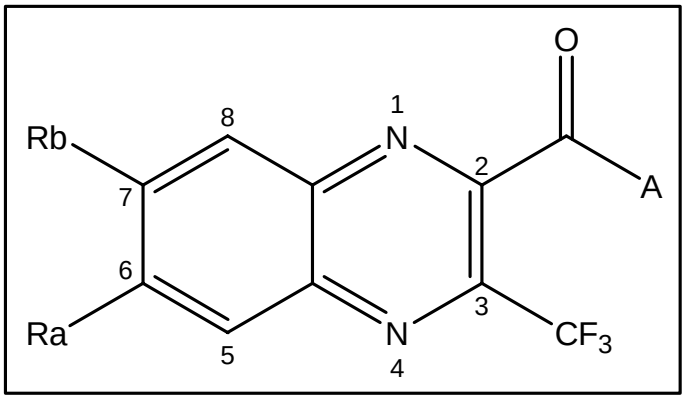
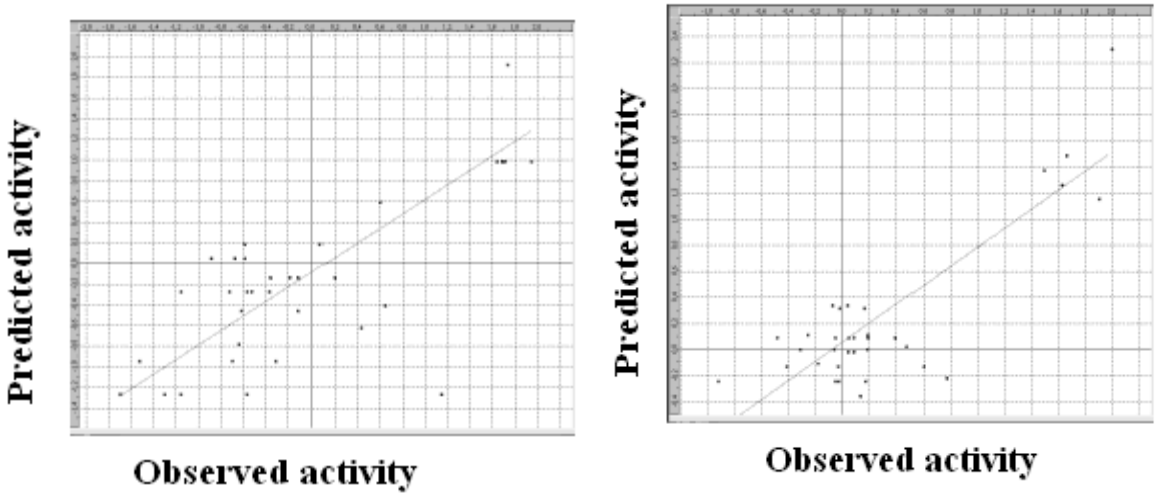
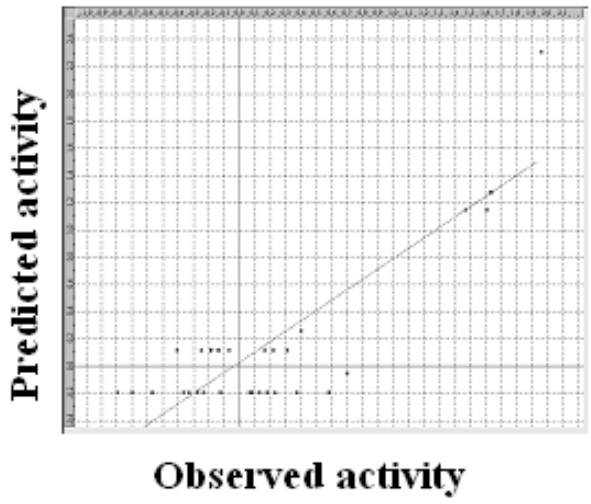


Fig1 Parent structure of quinoxaline derivatives

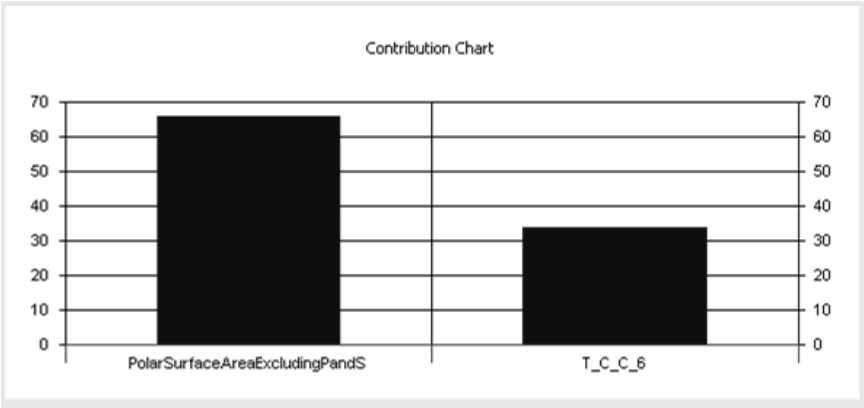


Model 1 **Model 2**

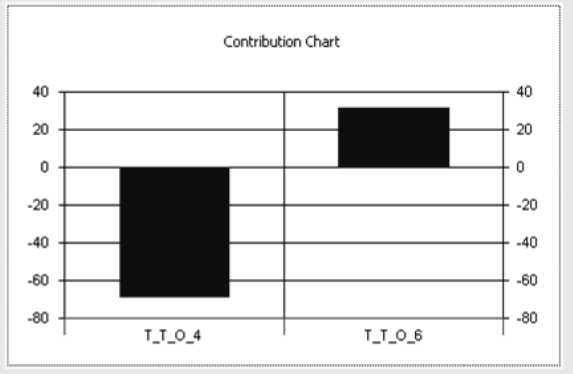


Model 3

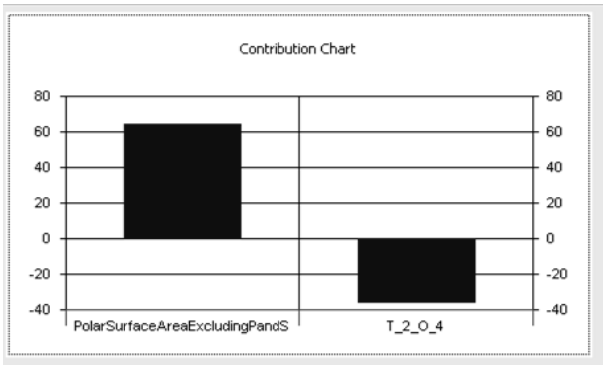
Fig.2 Graphs of observed v/s predicted activity of the models 1, 2, and 3.



Model 1



Model 2



Model 3

Fig.3 Contribution charts of the statistically significant models obtained through 2D QSAR analysis