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In Silico Study of Neurokinin-1 Receptor Antagonists by QSAR Modeling

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ABSTRACT

QSAR studies were performed on a series neurokinin-1 receptor. neurokinin-1 receptor have been analyzed in relation to their physicochemical and molecular properties. On the basis of QSAR studies presented here, the coefficients of Id, IOR, MR, MW, ST, MV, Pz are positive and therefore it may be suggested that denser, bulkier, more polar substituents with more vertices should have positive influence on the activity of NK_1 receptor. and the positive coefficients of $^0\chi$, $^1\chi$, $^2\chi$,$^3\chi$,$^4\chi$,$^5\chi$, W, W_A, and BAC parameters indicate that compounds, which are sterically hindered, are preferable for the activity of NK_1 receptor. The coefficient of hydrophobic parameter (LogP) was found to be negative and this clearly indicates that this parameter has negative influence in determining the activity , also the presence of group at R_1-position and (-CH_3) group at Z-position should be preferable and the presence of group at Y-position causes a substantial decrease in activity. The results are critically discussed on the basis of regression data and cross validation techniques. Poglani factor Q and the results of LOO (leave one out) method confirms the reliability and predictability of the proposed models.

Keywords: QSAR, BAC, PRESS/SSY

I. INTRODUCTION

Neurokinin (NK) receptors belong to G-protein coupled receptor and can be divided into three subtypes: NK_1, NK_2 and NK_3. They are located on submucosal enterocytes through the release of the both cholinergic and non cholinergic neurotransmitters. These NK_1 receptors have been implicated in many pathopysiological effects related to pulmonary dysfunction and many mental disorders such as anxiety and depression1. The current study represents the QSAR analysis of a series of NK_1 receptor antagonists[2] (Ki which represents NK_1 receptor affinities are reported in the literature) using a number of structural parameters alongwith different indicator parameters at different substitution sites.

II. Experimental

Hansch analysis[3] was used for multiparametric regression analysis. The multiparametric regression analysis used to derive the correlation was executed with the SPSS (7.5) programme. For QSAR studies, different analogues of parent structure and values of biological activity (pKi) are reported in Table1. The structural parameters used are equalized electronegativity (Xeq)[4], Polarizability (Pz) as electronic parameters, Partition coefficient (LogP)[5] as hydrophobic parameter, Density (D), Index of refraction (IOR), Molar refractivity (MR), Molecular weight (MW), Molar Volume (MV), Parachor (Pc), Surface tension (ST), Information Theoretic Index (Id) ,Weiner Index (W), Mean Weiner Index (WA), Balaban Index (J), Balaban centric index (BAC) and Conectivity indices($^0\chi$,$^1\chi$, $^2\chi$,$^3\chi$,$^4\chi$,$^5\chi$)[6] as steric parameters. The structural parameters are calculated with the help of ACD Lab[6] and DRAGON[7] software. A total of 21 descriptors were chosen for the QSAR analysis are listed in Table-2.

III. Monoparametric Models

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Where n is the number of data points, R^8 is the correlation coefficient, R^2 is coefficient of determination, R^2_A represents adjusted R^2 or explained variance in activity that can be accounted by the equation, SE is the standard error of estimate, F is the variance ratio between observed and calculated activities and data with in parenthesis are confidence interval at 95% level. On the basis of statistical parameters, it can be said that all the above equations in their present form are insignificant. All the physicochemical parameters and their square terms were taken together to check the parabolic relationship which was found to be absent.

The autocorrelation between all the structural parameters is shown in Table-4. A close study of this table makes it clear that there are a number of parameters which are orthogonal and, therefore, can be used together in multiparametric regression studies. Multiparametric Modeling[9] Using Indicator parameters-

In order to study the role of specific substituents at a particular position, three indicator parameters IR for at R_1- position, IY for at Y-position and IZ for ($-CH_3$) at Z-position were used.. The values for these dummy parameters are also listed in Table-1. It is taken one for that particular group or substituent and zero for all such cases were that group or substituent is absent. Different combination of physicochemical parameters and indicator parameters which have no autocorrelation were used and the statistically significant models obtained are summarized in Table-5 in the form of equations.

The statistical data listed in table show that all the given equations in Table-5 are significant and the set of physicochemical parameters and indicator parameters used may be useful for the future drug designing.

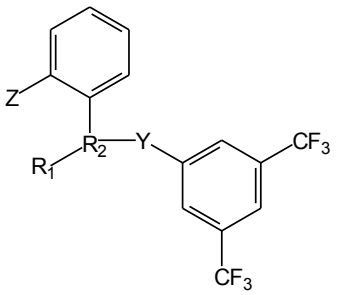
On the basis of QSAR studies presented above (Table-5), the coefficients of Id, IOR, MR, MW, ST, MV, Pz are positive and therefore it may be suggested that denser, bulkier, more polar substituents with more vertices should have positive influence on the activity of NK_1 receptor. Further, positive coefficients of $^0\chi$, $^1\chi$, $^2\chi$,$^3\chi$,$^4\chi$,$^5\chi$, W, W_A, and BAC parameters indicate that compounds, which are sterically hindered, are preferable for the activity of NK_1 receptor. The coefficient of hydrophobic parameter (Log P) was found to be negative which clearly indicates that this parameter has negative influence in determining the activity.

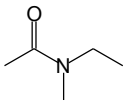
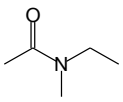
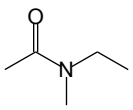
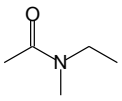
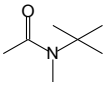
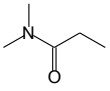
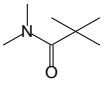
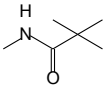
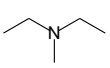
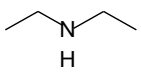
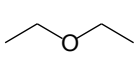
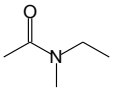
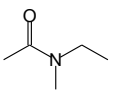
A very interesting and striking feature of the QSAR modeling[10-16] presented in this section reveals that everywhere the coefficient of IR and IZ are positive and for IY the coefficient is negative. This can be explained by suggesting that the presence of group at R_1-position and ($-CH_3$) group at Z-position should be preferable and at the same time while some other substituent may be tolerated. The presence of group at Y-position definitely causes a substantial decrease in activity.

In order to examine the relative potential of models, predictive correlation coefficient (R^2_{Pred})[11] were estimated by plotting graphs between observed and calculated pKi values obtained with the help of eqs1and eqs 2 . The comparison between observed and predicted activities is listed in Table- 6. Predictive ability was also evaluated by the LOO[12] (Leave one out) cross-validation procedure. This method systematically removes one data point at a time a model is constructed on the basis of this reduce data set and is subsequently used to predict the removed sample. This procedure was repeated for all the points until a complete set of predicted values was obtained. Various cross-validation parameters calculated for the proposed models are presented in Table- 8. PRESS (Predicted residual sum of squares) appears to be the most important cross-validation parameters accounting for good estimate of the real predictive error of the models. In case its value is less than SSY (Sum of the square of all response value), it will mean that the predictive power of the model is good and is not based upon chance and therefore, can be considered statistically significant.For a reasonable QSAR model[13-17], PRESS/SSY should be smaller than 0.400. In the present case, the ratio PRESS/SSY ranges between 0.108-0.131 indicating that all the proposed models are reliable. The PSE as well as S_{PRESS} are good parameters to be used for discussing the uncertainty in prediction. The lower the value of these parameters, the better will be the predictive ability of the model.

The indication of the performance of the model was also obtained from R^2_{cv} (the overall predictive ability). The highest R^2_{cv} (0.892) was found for QSAR model 2, indicating that it has an outstanding predictive power.

Table – 1. Biological activities and indicator Parameters of Neurokinin-1 Receptor Antagonists



S. No	Substituents				Observed pKi	Indicator Parameters		
	Z	R_1	R_2	Y		IZ	IR	IY
1.	H	H			7.2924	0	0	0
2.	CH_3	H			7.770	1	0	0
3.	Cl	H			7.658	0	0	0
4.	Br	H			7.347	0	0	0
5.	H	H			6.530	0	0	0
6.	H	H			6.250	0	0	0
7.	H	H			7.168	0	0	0
8.	H	H			5.860	0	0	1
9.	H	H			6.140	0	0	0
10.	H	H			6.430	0	0	0
11.	H	H			6.650	0	0	0
12.	CH_3	H			8.854	1	0	0
13.	CH_3	H			8.0710	1	0	0
14.	CH_3	H			8.469	1	0	0

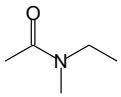
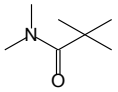
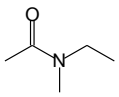
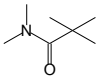
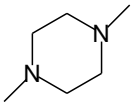
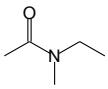
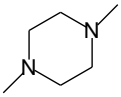
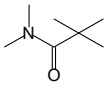
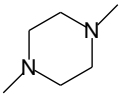
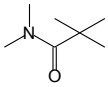
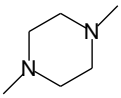
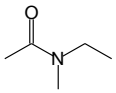
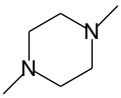
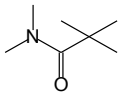
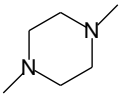
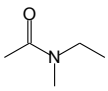
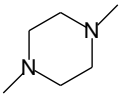
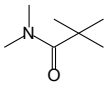
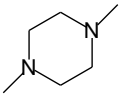
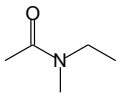
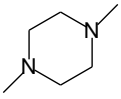
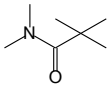
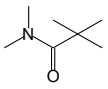
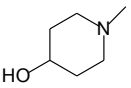
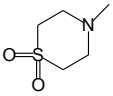
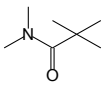
S. No	Substituents Z	R_1	R_2	Y	Observed pKi	Indicator Parameters IZ	IR	IY
15.	CH_3	H			8.337	1	0	0
16.	CH_3	H			4.402	1	0	0
17.	CH_3	H			8.420	1	0	0
18.	CH_3	H			7.776	1	0	0
19.	CH_3				9.237	1	0	0
20.	CH_3				9.022	1	0	0
21.	CH_3				8.770	1	0	0
22.	CH_3				8.208	1	0	0
23.	CH_3				8.699	1	0	0
24.	CH_3				8.456	1	0	0
25.	CH_3				8.959	1	0	0
26.	CH_3				8.770	1	0	0
27.	CH_3				9.357	1	0	0
28.	CH_3				9.699	1	1	0
29.	CH_3				9.301	1	0	0
30.	CH_3				9.097	1	0	0

Table 2. Physicochemical Parameters for a series of Neurokinin-1 Receptor Antagonists

S.No.	BAC	D	Id	IOR	J	LogP	MW	MR	MV	Pc	Pz	ST	W	WA	$^{0}\chi$	$^{1}\chi$	$^{2}\chi$	$^{3}\chi$	$^{4}\chi$	$^{5}\chi$	Xeq
1	69	1.295	4.832	1.526	1.653	4.690	437.378	103.670	337.700	817.800	41.090	34.300	2724	5.858	22.811	14.464	14.781	10.662	8.195	7.125	2.472
2	86	1.275	4.870	1.525	1.674	5.225	451.404	108.490	354.000	855.400	43.010	34.100	2948	5.944	23.681	14.875	15.309	11.135	8.560	7.382	2.456
3	86	1.349	4.870	1.533	1.674	5.285	471.822	108.560	349.600	853.700	43.040	35.500	2948	5.944	23.681	14.875	15.309	11.135	8.560	7.382	2.491
4	86	1.458	4.870	1.541	1.674	5.435	516.274	111.360	353.900	868.300	44.140	36.200	2948	5.944	23.681	14.875	15.309	11.135	8.560	7.382	2.482
5	105	1.252	4.900	1.517	1.786	5.750	465.431	112.510	371.600	889.200	44.600	32.700	3042	5.761	24.604	15.225	16.009	11.977	8.749	7.430	2.441
6	69	1.309	4.832	1.536	1.653	5.130	437.378	104.260	334.000	814.000	41.330	35.200	2724	5.858	22.811	14.464	14.781	10.662	8.195	7.125	2.472
7	105	1.265	4.900	1.526	1.786	6.190	465.431	113.100	367.900	885.500	44.830	33.500	3042	5.761	24.604	15.225	16.009	11.977	8.749	7.430	2.441
8	86	1.291	4.900	1.532	1.723	5.330	451.404	108.400	349.300	842.300	42.970	33.700	2876	5.798	23.734	14.798	15.595	11.358	8.213	7.218	2.456
9	54	1.248	4.792	1.520	1.592	6.440	423.394	103.190	339.000	809.200	40.900	32.400	2566	5.899	21.941	14.037	14.382	9.918	7.938	6.833	2.440
10	41	1.263	4.792	1.519	1.529	5.710	409.368	98.430	324.000	771.700	39.020	32.100	2414	5.946	21.071	13.643	13.736	9.665	7.533	6.595	2.456
11	41	1.275	4.752	1.512	1.529	6.040	410.352	96.580	321.600	763.400	38.280	31.700	2414	5.946	21.071	13.643	13.736	9.665	7.533	6.595	2.472
12	105	1.256	5.165	1.538	1.457	5.954	549.551	136.970	437.300	1085.100	54.300	37.900	5058	6.826	28.535	18.235	18.618	13.983	10.780	9.410	2.412
13	86	1.302	4.870	1.526	1.674	3.880	452.392	106.590	347.200	849.600	42.250	35.800	2948	5.944	23.681	14.875	15.309	11.135	8.560	7.382	2.464
14	126	1.272	4.937	1.526	1.804	5.500	480.445	116.020	377.400	917.300	45.990	34.800	3282	5.850	25.474	15.636	16.537	12.449	9.114	7.687	2.442
15	86	1.302	4.870	1.526	1.674	3.750	452.392	106.590	347.200	849.600	42.250	35.800	2948	5.944	23.681	14.875	15.309	11.135	8.560	7.382	2.472
16	126	1.272	4.937	1.526	1.804	4.000	480.445	116.020	377.400	917.300	45.990	34.800	3282	5.850	25.474	15.636	16.537	12.449	9.114	7.687	2.442
17	86	1.302	4.870	1.526	1.674	3.750	452.392	106.590	347.200	849.600	42.250	35.800	2948	5.944	23.681	14.875	15.309	11.135	8.560	7.382	2.472
18	126	1.272	4.937	1.526	1.804	5.250	480.445	116.020	377.400	917.300	45.990	34.800	3282	5.850	25.474	15.636	16.537	12.449	9.114	7.687	2.442
19	105	1.278	5.165	1.539	1.457	4.219	550.539	135.060	430.500	1080.700	53.540	39.600	5058	6.826	28.535	18.235	18.618	13.983	10.780	9.410	2.423
20	149	1.255	5.220	1.539	1.543	5.719	578.592	144.500	460.700	1157.100	57.280	39.700	5530	6.744	30.328	18.996	19.845	15.297	11.335	9.715	2.405
21	149	1.255	5.165	1.539	1.571	4.659	578.592	144.500	460.700	1157.100	57.280	39.700	5432	6.624	30.328	18.996	19.845	15.297	11.326	9.763	2.405
22	105	1.278	5.165	1.539	1.482	2.969	550.539	135.060	430.500	1080.700	53.340	39.600	4974	6.713	28.535	18.235	18.618	13.983	10.771	9.454	2.423
23	149	1.255	5.220	1.539	1.571	5.719	578.592	144.500	460.700	1157.100	57.780	39.700	5432	6.624	30.328	18.996	19.845	15.297	11.326	9.763	2.405
24	105	1.301	5.165	1.540	1.482	4.032	551.527	133.160	423.700	1076.200	52.780	41.600	4974	6.713	28.535	18.235	18.618	13.983	10.771	9.454	2.435
25	149	12.760	4.949	1.540	1.571	4.602	579.58	142.590	453.900	1152.700	56.520	41.500	5432	6.624	30.328	18.996	19.845	15.297	11.326	9.763	2.415
26	105	1.301	5.165	1.540	1.457	3.102	551.527	133.160	423.700	1076.200	52.780	41.600	5058	6.826	28.535	18.235	18.618	13.983	10.780	9.410	2.435
27	149	1.276	5.220	1.540	1.543	4.652	579.58	142.590	453.900	1152.700	56.520	41.500	5530	6.744	30.328	18.996	19.845	15.297	11.335	9.715	2.415
28	126	1.283	5.190	1.537	1.547	5.319	565.55	137.830	440.700	1111.000	54.640	40.300	5127	6.573	29.457	18.602	19.224	14.886	11.184	9.491	2.423
29	149	1.297	5.258	1.550	1.542	4.725	579.577	142.420	446.600	1145.800	56.460	43.200	5530	6.744	30.328	18.996	19.845	15.297	11.335	9.715	2.413
30	174	1.344	5.244	1.547	1.542	5.279	613.615	144.900	456.200	1170.800	57.440	43.300	5935	6.893	31.25	19.309	20.827	15.62	11.471	9.907	2.434

Table 3. Monoparametric Models

S. No.	Equation	n	R	R^2	R^2_A	SE	$F_{1,28}$
1	$pKi=2.385\times10^{-2}(\pm7.850\times10^{-3})BAC+5.503$	30	0.757	0.573	0.557	0.718	37.534
2	pKi= -0.945 (±10.350)D+9.251	30	0.35	0.001	0.034	1.098	0.035
3	pKi= 5.084 (±1.513)Id-17.389	30	0.793	0.629	0.615	0.670	47.384
4	pKi= 76.381 (±34.162) IOR-109.008	30	0.428	0.408	0.831	0.831	20.975

Table 4. Correlation Matrix demonstrating correlation between physicochemical parameters with indicator parameters

	IZ	IR	IY	BAC	D	Id	IOR	J	LogP	MR	MV	MW	Pc	Pz	ST	W	WA	$^{0}\chi$	$^{1}\chi$	$^{2}\chi$	$^{3}\chi$	$^{4}\chi$	$^{5}\chi$	Xeq
IZ	1.000																							
IR	0.131	1.000																						
IY	-0.263	-0.034	1.000																					
BAC	0.670	0.110	-0.111	1.000																				
D	-0.213	-0.026	0.011	-0.095	1.000																			
Id	0.022	0.079	0.008	0.275	0.033	1.000																		
IOR	0.477	0.095	-0.007	0.681	0.320	0.317	1.000																	
J	-0.286	-0.012	0.182	-0.084	0.063	-0.220	-0.501	1.000																
LogP	-0.532	0.081	0.083	-0.127	-0.143	-0.109	-0.289	0.190	1.000															
MR	0.674	0.180	-0.150	0.865	-0.148	0.347	0.817	-0.540	-0.186	1.000														
MV	0.682	0.186	-0.162	0.867	-0.195	0.341	0.760	-0.526	-0.172	0.998	1.000													
MW	0.646	0.184	-0.162	0.862	0.041	0.355	0.871	-0.525	-0.212	0.981	0.972	1.000												
Pc	0.690	0.187	-0.167	0.862	-0.150	0.348	0.811	-0.552	-0.211	0.999	0.997	0.980	1.000											
Pz	0.674	0.180	-0.150	0.865	-0.148	0.347	0.817	-0.540	-0.185	1.000	0.998	0.981	0.999	1.000										
ST	0.681	0.172	-0.160	0.759	0.112	0.344	0.904	-0.611	-0.414	0.910	0.890	0.937	0.921	0.910	1.000									
W	0.680	0.179	-0.162	0.820	-0.134	0.350	0.823	-0.627	-0.231	0.990	0.986	0.974	0.994	0.990	0.938	1.000								
WA	0.630	0.141	-0.197	0.626	-0.091	0.325	0.792	-0.619	-0.275	0.913	0.905	0.902	0.921	0.913	0.913	0.954	1.000							
$^{0}\chi$	0.633	0.604	-0.132	0.777	-0.124	0.315	0.704	-0.449	-0.149	0.888	0.889	0.877	0.892	0.888	0.824	0.880	0.788	1.000						
$^{1}\chi$	0.490	0.193	-0.107	0.534	-0.003	0.241	0.592	-0.434	-0.164	0.650	0.642	0.659	0.658	0.650	0.685	0.674	0.668	0.624	1.000					
$^{2}\chi$	0.753	0.161	-0.145	0.855	-0.131	0.347	0.729	-0.390	-0.290	0.903	0.903	0.890	0.907	0.903	0.851	0.895	0.802	0.819	0.607	1.000				
$^{3}\chi$	0.698	0.204	-0.132	0.912	-0.157	0.348	0.797	-0.449	-0.208	0.991	0.990	0.972	0.991	0.991	0.904	0.976	0.870	0.902	0.652	0.918	1.000			
$^{4}\chi$	0.714	0.212	-0.189	0.852	-0.138	0.341	0.817	-0.556	-0.253	0.995	0.992	0.978	0.998	0.995	0.933	0.993	0.925	0.903	0.671	0.911	0.989	1.000		
$^{5}\chi$	0.701	0.188	-0.167	0.817	-0.127	0.341	0.830	-0.611	-0.274	0.991	0.986	0.975	0.994	0.991	0.941	0.996	0.947	0.885	0.671	0.900	0.977	0.997	1.000	
Xeq	-0.548	-0.099	0.104	-0.794	0.300	-0.274	-0.564	0.434	-0.045	-0.848	-0.855	-0.808	-0.846	-0.848	-0.706	-0.848	-0.768	-0.731	-0.548	-0.777	-0.843	-0.825	-0.817	1.000

Table 5. Multiparametric Models Using Indicator Parameters

S. No.	Equation	n	R	R^2	R_A	SE	$F_{5,24}$
1.	pKi= 3.754 (±3.601) D + 2.377 (±1.156) Id + 1.313 (± 0.419) IZ - 1.078 (±0.809) IY + 0.789 (±0.795) IR - 9.557	30	0.950	0.903	0.883	0.370	44.595
2.	pKi= -8.39 × 10^{-2} (±4.342) D + 39.466 (±21.259) IOR + 1.415 (± 0.413) IZ - 1.225 (±0.854) IY + 1.001 (±0.817) IR - 53.269	30	0.946	0.894	0.872	0.386	40.667
3.	pKi= 4.005 (±4.481) D - 1.433 (±1.675) J + 1.796 (± 0.405) IZ - 0.827 (±1.009) IY + 0.996 (±0.979) IR + 3.986	30	0.922	0.849	0.818	0.460	27.078
4.	pKi= 3.409 (±4.383) D + 8.853 × 10^{-2} (±8.353 × 10^{-2}) $^1\chi$ + 1.655 ± 0.437) IZ - 0.960 (±0.974) IY + 0.915 (±0.958) IR + 1.109	30	0.926	0.858	0.828	0.447	29.012
5.	pKi= 1.102 (±1.763) Id + 26.638 (±26.896) IOR + 1.282(± 0.418) IZ - 1.210 (±0.819) IY + 0.894 (±0.808) IR - 39.138	30	0.949	0.901	0.881	0.373	43.817

Table 6. Comparison between observed and predicted values for proposed models

PKi					
S.No.	Observed	Equation – 1		Equation - 2	
		Predicted	Residual	Predicted	Residual
1.	7.292	6.790	0.502	6.847	0.446
2.	7.770	8.119	-0.350	8.226	-0.457
3.	7.658	7.084	0.574	7.122	0.536
4.	7.347	7.493	-0.146	7.436	-0.889
5.	6.530	6.791	-0.261	6.493	0.037
6.	6.250	6.843	-0.592	7.239	-0.989
7.	7.168	6.840	0.327	6.847	0.321
8.	5.860	5.860	.000	5.860	0.000
9.	6.140	6.520	-0.380	6.611	-0.471
10.	6.430	6.577	-0.147	6.572	-0.143
11.	6.650	6.526	0.124	6.297	0.353
12.	8.854	8.750	0.104	8.736	0.117
13.	8.071	8.221	-0.150	8.265	-0.195
14.	8.469	8.267	0.202	8.265	0.203
15.	8.337	8.221	0.117	8.265	0.072
16.	8.402	8.267	0.135	8.265	0.136
17.	8.420	8.221	0.200	8.265	0.155
18.	7.796	8.267	-0.471	8.265	-0.469
19.	9.237	8.833	0.404	8.776	0.461
20.	9.022	8.876	0.146	8.776	0.247
21.	8.770	8.746	0.023	8.776	-0.006
22.	8.208	8.833	-0.625	8.776	-0.568
23.	8.699	8.876	-0.177	8.776	-0.077
24.	8.456	8.919	-0.483	8.815	-0.359
25.	8.959	9.312	0.647	8.815	0.144
26.	8.770	8.919	-0.149	8.815	-0.045
27.	9.357	8.955	0.401	8.815	0.542
28.	9.699	9.699	0.000	9.699	0.000
29.	9.301	9.124	0.177	9.208	0.093
30.	9.097	9.267	-0.170	9.090	0.007

Table 7. Some Statistical techniques prove predictive ability for proposed models

S.No.	Model No.	Q	K	E	PE	6PE
1.	1	2.503	0.326	67.4	0.013	0.078
2.	2	2.568	0.311	68.9	0.012	0.072
3.	3	2.451	0.326	67.4	0.013	0.078
4.	4	2.544	0.315	68.5	0.012	0.072
5.	5	2.327	0.341	65.9	0.014	0.084

Table 8. Cross validation parameters for proposed models

S.No.	Model No.	PRESS	SSY	PRESS/SSY	R^2_{cv}	PSE	S_{PRESS}
1.	1	3.568	30.224	0.118	0.882	0.345	0.378
2.	2	3.284	30.501	0.108	0.892	0.331	0.370
3.	3	3.567	30.224	0.118	0.882	0.345	0.386
4.	4	3.336	30.456	0.110	0.890	0.333	0.373
5.	5	3.908	29.884	0.131	0.869	0.361	0.404

IV. CONCLUSION

On the basis of above discussions, it becomes evident that multiparametric models represented by QSAR equations are statistically significant models and they are reliable and have good predictive ability and therefore it can be concluded that the coefficients of Id, IOR, D are positive and therefore denser, bulkier should have positive influence on the activity of NK_1 receptor whereas the positive coefficient of $^1\chi$ parameter indicate that compounds, which are sterically hindered, are preferable for the activity of NK_1 receptors.

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