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QSAR Study on the Affinity of Some Arylpiperazines towards the 5-HT$_{1A}$/α_1-Adrenergic Receptor Using the E-State Index

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Abstract—QSAR models represent the relationship of biological activity with either physicochemical parameters or structural indices. QSAR study was performed on some arylpiperazines as 5-HT$_{1A}$/α_1-adrenergic receptor antagonists using E-state indices to identify the pharmacophoric requirements. It was found that some of the atoms played important roles to both activities and some played important role in selectivity of compound to the 5-HT$_{1A}$ antagonistic activity. The presence of COONHPr group at the *ortho*-position of the phenyl ring might be disadvantageous and Br at *meta*-position might be conducive to the activity. COOPr at the *ortho*-position might be disfavored the adrenergic α_1-antagonistic activity, thus increase the selectivity.

Drugs elicit their biological response by interacting with specific targets, which may be enzymes, receptors, ion channels, nucleic acids or any other biological macromolecules.[1] This interaction is governed by the collective effect of the electronic and topological structure. Traditionally, atom-level description of structure have been composed of two parts—one is a statement of electronic composition or probability and the other is some quantitation of the steric environment or topology. Topology is a complex result of electronic structure, which can be described as the Electrotopological State of an atom. The electrotopological state of an atom is a nonemperical index encoding the electronegativity of the atom, the inductive influence of other atoms in the chemical graph and its topological state. The derivation of this index is called the E-state index.[2]

The E-state value of each atom contains electronic and topological structure information from all other atoms within the structure.[3–6]

This development of non-emperical structure descriptors has followed the direction of whole molecule index generation from constituent atom or bond attributes. The most widely used example is the set of molecular connectivity indexes developed by Keir and Hall. These have been quite successful in analyzing molecular properties in Quantitative Structure–Activity Relationships (QSARs).[7]

In QSAR models, molecular structure has been represented with either physical properties such as the partition coefficient or structure indices such as molecular connectivity (chi) indices. These structure representations have been largely based on the whole molecule. In this way, QSAR model offers some insight into drug pharmacophore. Pharmacophore is a pattern of atoms on an active molecule that is essential for this activity. The patterns include the electronic structure of key atoms or bonds plus the spatial arrangement or topology of these features within the molecule. By altering different features in a lead compound, it is possible to build a pattern that constitutes a putative pharmacophore.[8]

Serotonin (5-hydroxytryptamine) is one of the most attractive targets for a medicinal chemist. About 90% of the body's content of 5-HT is localized in the intestines; most of the rest is in platelets and in the brain. 5-HT is a potent depolarizer of the nerve endings. It thus exerts direct as well as reflex and indirect effects. Serotonergic receptors are classified by isolation of distinct receptor, their cloning and ligand-binding studies. There are three

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major types of serotonergic receptors, 5-HT_1, 5-HT_2 and 5-HT_3 and four subtypes of 5-HT_1 receptor. Among 5-HT receptors, 5-HT_{1A} subtype is responsible for psychiatric disorders such as anxiety and depression. There are several structurally different compounds which bind the 5-HT_{1A} receptor site; among them arylpiperazine derivatives represent one of the most important classes of the 5-HT_{1A} receptor ligand. In general, 5-HT antagonists are mostly non-selective and interact with several others receptors such as the α_1-adrenergic receptor. In this regard, QSAR studies have been performed using ETSA indices to evaluate the structural requirements of arylpiperazine that are responsible for 5-HT_{1A}/α_1 selectivity.[9–11]

In this present study, which is part of our programme of rational drug design,[12–19] attempts have been made to perform QSAR studies on some 5-HT_{1A}/α_1-adrenergic receptor antagonists reported by Lopez-Rodriguez et al.[20] using the E-state index in this article to identify pharmacophoric requirements responsible for the antagonistic activity. Previous attempts at QSAR were made to perform Hansch analysis as well as that of artificial neural networks and computational simulation of ligand recognition by Lopez-Rodriguez et al.[20] to find out some other aspects of these compounds in relation to bioactivity. Activity data of these compounds are shown in Table 1 (Fig. 1).

Table 1. 5-HT_{1A} and α_1-adrenergic receptor binding data

Compd	x	y	z	R	5-HT_{1A}		α_1	
					K_1 (nm)	pK_1[a]	K_2 (nm)	pK_2[a]
1	0	0	0	*o*-OBu	15	7.82	6.4	8.19
2	0	0	0	*o*-CONHPr	808	6.09	608	6.22
3	0	0	0	*m*-NH_2	1182	5.93	393	6.41
4	0	0	0	*m*-Br	34	7.47	25	7.61
5	0	1	0	*o*-CH_3	220	6.66	5.7	8.25
6	0	1	0	*o*-COOPr	46	7.34	13	7.89
7	0	1	0	*o*-CN	65	7.19	8.2	8.09
8	0	1	0	*m*-NHCOPr^i	776	6.11	4430	5.35
9	1	0	0	*o*-CH_3	48	7.31	17	7.76
10	1	0	0	*o*-COOPr	55	7.26	12	7.93
11	1	0	0	*o*-CN	27	7.56	17	7.76
12	1	0	0	*m*-NHCOPr^i	266	6.57	1440	5.84
13	1	1	0	*o*-CH_3	143	6.84	29	7.53
14	1	1	0	*o*-OBu	92	7.04	13	7.89
15	1	1	0	*o*-CONHPr	4614	5.34	811	6.09
16	1	1	0	*o*-CF_3	179	6.75	339	6.47
17	0	0	1	*o*-CH_3	16	7.78	7.0	8.15
18	0	0	1	*o*-COOPr	4.8	8.32	41	7.39
19	0	0	1	*o*-CN	4.0	8.4	4.9	8.31
20	0	0	1	*m*-NHCOPr^i	193	6.72	5425	5.27
21	0	1	1	*o*-OBu	2.2	8.66	5.0	8.30
22	0	1	1	*o*-CONHPr	378	6.42	521	6.28
23	0	1	1	*m*-NH_2	68	7.17	231	6.64
24	0	1	1	*m*-Br	5.4	8.27	5.9	8.23
25	1	0	1	*o*-CH_3	12	7.92	25	7.59
26	1	0	1	*o*-OBu	8.7	8.06	10.5	7.98
27	1	0	1	*o*-CONHPr	1232	5.91	1354	5.87
28	1	0	1	*o*-CF_3	5.5	8.26	72	7.14
29	1	1	1	*o*-CH_3	32	7.5	27	7.56
30	1	1	1	*o*-COOPr	28	7.55	392	6.41
31	1	1	1	*o*-CN	15	7.82	30	7.52
32	1	1	1	*m*-NHCOPr^i	198	6.70	16140	4.79

[a]pK_1 and pK_2 are calculated from K_1 and K_2 in Molar concentrations, respectively.

The E-state indices of the common atoms were calculated using program 'Mouse' developed in our laboratory and some of the important values of that as well as indicator parameters are shown in Table 2.

Correlation analysis was carried out among E-state indices of common atoms and biological activities and the correlation matrix of sum of the important indices is presented in Table 3.

Depending on the individual correlation of E-state indices with activities and intercorrelation between the indices, regression analysis[21] was carried out using 'Multi Regress', a statistical programme developed in our laboratory. 5-HT_{1A} receptor antagonistic activity was found to have best correlation with E-state indices

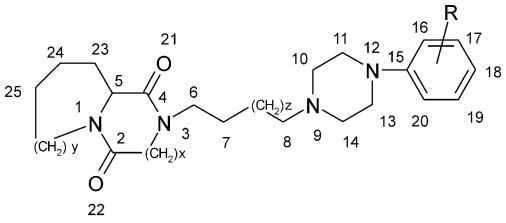

Figure 1. The general structure of arylpiperazines.

Table 2. The value of important E-state indices and indicator parameters

Compd	S_8[a]	S_{10}[b]	S_{16}[c]	S_{21}[d]	I_1[e]	I_2[f]	I_3[g]
1	0.920	0.986	0.986	12.436	0	0	0
2	0.869	0.904	0.740	12.442	1	0	0
3	0.923	0.991	2.019	12.339	0	0	0
4	0.938	1.017	2.157	12.345	0	1	0
5	0.947	1.032	1.335	12.506	0	0	0
6	0.856	0.883	0.630	12.589	0	0	1
7	0.884	0.927	0.729	12.508	0	0	0
8	0.889	0.943	2.035	12.580	0	0	0
9	0.994	1.053	1.341	12.577	0	0	0
10	0.903	0.904	0.636	12.660	0	0	1
11	0.930	0.947	0.735	12.579	0	0	0
12	0.935	0.964	2.041	12.651	0	0	0
13	0.964	1.001	0.930	12.747	0	0	0
14	0.967	1.006	0.994	12.812	0	0	0
15	0.912	0.920	0.734	12.819	1	0	0
16	0.808	0.763	1.210	12.716	0	0	0
17	1.046	1.075	1.347	12.338	0	0	0
18	0.955	0.926	0.642	12.411	0	0	1
19	0.983	0.969	0.741	12.340	0	0	0
20	0.988	0.986	2.045	12.404	0	0	0
21	1.019	1.028	1.000	12.564	0	0	0
22	0.968	0.946	0.754	12.568	1	0	0
23	1.022	1.034	2.033	12.478	0	0	0
24	1.037	1.059	2.172	12.484	0	1	0
25	1.047	1.037	0.941	12.576	0	0	0
26	1.049	1.043	1.005	12.635	0	0	0
27	0.998	0.961	0.759	12.639	1	0	0
28	0.891	0.800	1.219	12.550	0	0	0
29	1.076	1.089	1.353	12.715	0	0	0
30	0.985	0.940	0.648	12.788	0	0	1
31	1.013	0.984	0.747	12.717	0	0	0
32	1.017	1.000	2.054	12.780	0	0	0

[a,b,c,d]E-state indices of atom nos 8, 10, 16 and 21, respectively.
[e,f,g]Indicator parameters for presence of CONHPr group at the *ortho*-position, Br at the *meta*-position and COOPr at the *ortho*-position of the phenyl ring, respectively.

Table 3. Correlation matrix of different important E-state indices, indicator parameters and activities

	S_8	S_{10}	S_{16}	S_{21}	I_1	I_2	I_3	pK_1	pK_2
S_8	1.00	0.14	−0.07	−0.01	0.07	−0.05	−0.07	0.32	0.21
S_{10}		1.00	0.34	−0.16	−0.21	0.24	−0.31	0.21	0.28
S_{16}			1.00	−0.27	−0.32	0.45	−0.40	−0.16	−0.37
S_{21}				1.00	0.12	−0.28	0.11	−0.24	−0.23
I_1					1.00	−0.10	−0.14	−0.59	−0.39
I_2						1.00	−0.10	0.21	0.20
I_3							1.00	0.19	0.10
pK_1								1.00	0.69
pK_2									1.00

of atoms 8, 16, 21—S_8, S_{16} and S_{21}, respectively, and two other indicator parameters I_1, I_2, which represent presence of CONHPr group at ortho position and Br at meta position of the phenyl ring respectively as shown in eq 1:

$$pK_1 = 23.588\ (\pm 7.988) + 0.012\ (\pm 0.005)S_8 - 0.885\ (\pm 0.189)\ S_{16} - 1.210\ (\pm 0.632)\ S_{21} - 1.730\ (\pm 0.275)I_1 + 1.209\ (\pm 0.404)I_2 \quad (1)$$

$n = 32$; $R = 0.845$; %EV = 71.40; $R^2_A = 0.659$; $F(5, 26) = 12.988$; $p < 0.0000$; S.E.E. = 0.483

where n is number of data points, R is correlation coefficient, %EV, R^2_A, F, p, S.E.E. are percentage of explained variance, adjusted R^2, ratio between the variances of observed and calculated activities, probability factor related to F-ratio and standard error of estimate respectively. Eq 1 explains 71.40% of the variances in the activity data. Positive coefficient of S_8 indicates that high value of S_8 is conducive to the activity whereas negative coefficients of S_{16} and S_{21} indicate that the high values of these are detrimental to the activity. Negative coefficient of I_1 and positive coefficient of I_2 suggest that CONHPr at the *ortho*-position may be detrimental to the activity and Br at the *meta*-position of the phenyl ring may be favorable to the activity, respectively.

After deletion of the outliers which might be acting through a different mechanism of action, eqs 2 and 3 were produced:

$$pK_1 = 22.981(\pm 7.525) + 0.012(\pm 0.005)\ S_8 - 0.883 \times (\pm 0.178)\ S_{16} - 1.165\ (\pm 0.595)\ S_{21} - 1.692\ (\pm 0.259)I_1 + 1.254\ (\pm 0.381)I_2 \quad (2)$$

$n = 31$; DC = 28; $R = 0.862$; %EV = 74.30; $R^2_A = 0.692$; $F(5, 25) = 14.428$; $p < 0.0000$; S.E.E. = 0.454

$$pK_1 = 20.532\ (\pm 5.113) + 5.044\ (\pm 0.911)\ S_8 - 0.973\ (\pm 0.121)\ S_{16} - 1.347\ (\pm 0.404)\ S_{21} - 1.598\ (\pm 0.176)\ I_1 + 1.183(\pm 0.258)I_2 \quad (3)$$

$n = 30$; DC = 28, 21; $R = 0.934$; %EV = 87.30; $R^2_A = 0.846$; $F(5, 24) = 32.794$; $p < 0.0000$; S.E.E. = 0.308

where DC is the deleted compound behaves as outliers may act through a different mechanism of action. The statistical quality of eq 3 was found to be of significant. It explains 87.30% of the variances in the activity data.

Similarly, regression equations are developed for α_1-adrenergic receptor antagonistic activity. Instead of S_8, for the 5-HT_{1A} receptor discussed earlier, which is having good correlation with pK_1, S_{10} (E-state index of atom 10) was used with S_{16}, S_{21}, I_1 (*o*-CONHPr) for the development of QSAR equation as shown below

$$pK_2 = 31.556\ (\pm 10.768) + 5.221(\pm 1.707)\ S_{10} - 1.382\ (\pm 0.238)\ S_{16} - 2.197\ (\pm 0.832)\ S_{21} - 1.560\ (\pm 0.367)\ I_1 \quad (4)$$

$n = 32$; $R = 0.807$; %EV = 65.18; $R^2_A = 0.600$; $F(4, 27) = 12.634$; $p < 0.0000$; S.E.E. = 0.646

Eq 4 explains 65.18% of the variances in the activity data. Positive coefficient of S_{10} indicates that higher value of S_{10} is conducive to the activity. The higher value of S_{16} and S_{21} are detrimental to the α_1-adrenergic receptor antagonistic activity as supported by their negative coefficients. The negative coefficient of I_1 suggests that CONHPr at the *ortho*-position may be detrimental to the activity.

Inclusion of another indicator parameter I_2 (*m*-Br) improved statistical quality of the QSAR model as shown in eq 5

$$pK_2 = 26.139\ (8.839) + 4.719\ (\pm 1.389)\ S_{10} - 1.689\ (\pm 0.209)\ S_{16} - 1.705\ (\pm 0.686)\ S_{21} - 1.649\ (\pm 0.298)\ I_1 + 1.709\ (\pm 0.440)\ I_2 \quad (5)$$

$$n = 32; \quad R = 0.883; \quad \%EV = 77.97; \quad R^2_A = 0.737; \quad F(5, 26) = 18.399; \quad p < 0.0000; \quad S.E.E. = 0.523$$

The positive coefficient of I_2 points out that the presence of Br at the *meta*-position may be conducive to the activity.

The addition of another indicator parameter I_3 for the presence of COOPr at the *ortho*-position of the phenyl ring significantly improved the statistical quality of the model.

$$pK_2 = 26.956\ (\pm 8.098) + 3.841(\pm 1.321)\ S_{10} - 1.915\ (\pm 0.212)\ S_{16} - 1.671\ (\pm 0.628)\ S_{21} - 1.907\ (\pm 0.292) I_1 + 1.871\ (\pm 0.408) I_2 - 0.756\ (\pm 0.308)\ I_3 \quad (6)$$

$$n = 32; \quad R = 0.907; \quad \%EV = 82.25; \quad R^2_A = 0.780; \quad F(6, 25) = 19.304; \quad p < 0.0000; \quad S.E.E. = 0.479$$

Eq 6 explains 82.25% of the variances in the activity data. The negative coefficient of I_3 indicates that the presence of COOPr at the *ortho*-position of phenyl ring may be disadvantageous to the activity.

The observed, calculated and residual activities for eqs 3 and 6 are listed in Table 4. Eqs 3 and 6 are validated by the Leave-One-Out (LOO) cross-validation method.[22] LOO-predicted value, predictive residual value for eqs 3 and 6 are presented in Table 5. Cross-validated parameters like cross-validated R^2 (q^2), predicted residual sum of squares (PRESS), sum of squares of regression values (SSY), uncertainty factor (S_{PRESS}) and predictive standard error (P.S.E.) are listed in Table 6. The significant values of q^2 of eqs 3 and 6 proved the model validation to predict the activities of the compounds.

From these QSAR studies, it has been found that atom no. 16, 21 are important for both activities. Atom no. 8 is important for serotonergic antagonism, where as atom no. 10 is important for adrenergic antagonism. Atom no. 16 belongs to the phenyl ring, in which substitutions may affect the value of S_{16}. Thus, substitutions with high intrinsic effect at the *ortho*- and *meta*-positions may

Table 4. Observed, calculated, residual activities of eqs 3 and 6

Compd	Eq 3			Eq 6		
	Obsd	Calcd	Resd	Obsd	Calcd	Resd
1	7.820	7.464	0.356	8.190	8.070	0.120
2	6.090	5.841	0.249	6.220	6.310	−0.090
3	5.930	6.605	−0.675	6.410	6.274	0.136
4	7.470	7.721	−0.251	7.610	7.970	−0.360
5	6.660	7.166	−0.506	8.250	7.462	0.788
6	7.340	7.282	0.058	7.890	7.344	0.546
7	7.190	7.436	−0.246	8.090	8.216	−0.126
8	6.110	6.094	0.017	5.350	5.656	−0.306
9	7.310	7.302	0.008	7.760	7.412	0.348
10	7.260	7.417	−0.157	7.930	7.295	0.635
11	7.560	7.566	−0.006	7.760	8.162	−0.402
12	6.570	6.224	0.346	5.840	5.606	0.234
13	6.840	7.322	−0.482	7.530	7.715	−0.185
14	7.040	7.187	−0.147	7.890	7.503	0.387
15	5.340	5.556	−0.216	6.090	5.753	0.337
16	6.750	6.304	0.446	6.470	6.317	0.153
17	7.780	7.880	−0.100	8.150	7.885	0.265
18	8.320	8.009	0.311	7.390	7.784	−0.394
19	8.400	8.150	0.250	8.310	8.635	−0.328
20	6.720	6.820	−0.100	5.270	6.096	−0.826
21[a]	8.660	—	—	8.300	7.991	0.309
22	6.420	6.157	0.263	6.280	6.234	0.046
23	7.170	6.903	0.267	6.640	6.180	0.460
24	8.270	8.019	0.251	8.230	7.870	0.360
25	7.920	7.960	−0.040	7.590	8.118	−0.528
26	8.060	7.828	0.232	7.980	7.920	0.060
27	5.910	6.207	−0.298	5.870	6.163	−0.293
28[a]	8.260	—	—	7.140	6.719	0.421
29	7.500	7.518	−0.018	7.560	7.297	0.263
30	7.550	7.647	−0.097	6.410	7.196	−0.786
31	7.820	7.787	0.033	7.520	8.051	−0.531
32	6.700	6.451	0.249	4.790	5.504	−0.714

[a]Outliers for eq 3.

Table 5. LOO-predicted (Pred.) and predictive residual (Pres.) values for eqs 3 and 6

Compd	Eq 3			Eq 6		
	Obsd	Pred.	Pres.	Obsd	Pred.	Pres.
1	7.820	7.425	0.395	8.190	8.057	0.133
2	6.090	5.715	0.375	6.220	6.351	−0.131
3	5.930	6.805	−0.875	6.410	6.236	0.174
4	7.470	8.002	−0.532	7.610	8.348	−0.738
5	6.660	7.195	−0.535	8.250	7.404	0.847
6	7.340	7.269	0.071	7.890	7.155	0.735
7	7.190	7.473	−0.283	8.090	8.237	−0.147
8	6.110	6.088	0.022	5.350	5.717	−0.367
9	7.310	7.302	0.008	7.760	7.382	0.378
10	7.260	7.439	−0.179	7.930	7.078	0.852
11	7.560	7.567	−0.007	7.760	8.216	−0.456
12	6.570	6.147	0.423	5.840	5.557	0.283
13	6.840	7.373	−0.533	7.530	7.742	−0.212
14	7.040	7.210	−0.170	7.890	7.428	0.462
15	5.340	5.661	−0.321	6.090	5.594	0.496
16	6.750	6.116	0.634	6.470	6.197	0.273
17	7.780	7.907	−0.127	8.150	7.822	0.328
18	8.320	7.952	0.368	7.390	7.969	−0.579
19	8.400	8.086	0.314	8.310	8.725	−0.415
20	6.720	6.842	−0.122	5.270	6.282	−1.012
21	8.660	—	—	8.300	7.964	0.336
22	6.420	6.062	0.358	6.280	6.218	0.062
23	7.170	6.849	0.321	6.640	6.088	0.552
24	8.270	7.738	0.532	8.230	7.492	0.738
25	7.920	7.965	−0.046	7.590	8.175	−0.585
26	8.060	7.797	0.263	7.980	7.914	0.066
27	5.910	6.325	−0.415	5.870	6.265	−0.395
28	8.260	—	—	7.140	6.534	0.606
29	7.500	7.522	−0.022	7.560	7.243	0.317
30	7.550	7.664	−0.114	6.410	7.551	−1.141
31	7.820	7.783	0.037	7.520	8.133	−0.613
32	6.700	6.366	0.333	4.790	5.741	−0.951

Table 6. Cross-validated parameters for eqs 3 and 6

Equation	PRESS	SSY	q^2	S_{PRESS}	PSE
3	3.894	17.787	0.781	0.162	0.130
6	9.913	32.320	0.693	0.397	0.310

contribute to activities. Atom no. 21, which is cyclic carbonyl oxygen atom, disfavors both activities. It may be due to its electronic effect, which hindrance its binding to the receptor site. From the point of the selectivity of these compounds to the 5-HT_{1A} receptor than α_1-adrenergic receptor, atom nos 8 and 10 are important. Atom no. 8 favors 5-HT_{1A} antagonistic activity while atom no. 10 is the most important for α_1-adrenergic antagonistic activity. Addition of some substitutions with a high intrinsic factor, which reduces the value of S_{10}, may increase the selectivity of these arylpiperazines. The presence of COONHPr group at the *ortho*-position might be disadvantageous to both activities while the presence of Br at the *meta*-position might be conducive to the activity. COOPr at the *ortho*-position might be disfavored the α_1-adrenergic antagonistic activity, and thus increase the selectivity.

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References and Notes

1. Wolff, M. E. *Burger's Medicinal Chemistry, 5th ed*; Wiley-Interscience: New York, 1995; p 342.
2. Rose, K.; Hall, L. H.; Kier, L. B. *J. Chem. Inf. Comput. Sci*. **2002**, *42*, 651.
3. Kier, L. B.; Hall, L. H. *Molecular Structure Description: The Electrotopological State*; Academic Press: San Diego, CA, 1999; p 178.
4. Roy, K.; De, A. U.; Sengupta, C. *Drug Des. Discov*. **2002**, *18*, 33.
5. Roy, K.; Pal, D. K.; Sengupta, C. *Drug Des. Discov*. **2001**, *17*, 207.
6. Roy, K.; Pal, D. K.; Sengupta, C. *Drug Des. Discov*. **2000**, *17*, 183.
7. Kier, L. B.; Hall, L. H. *J. Mol. Graph. Mod*. **2001**, *20*, 76.
8. de Gregorio, C.; Kier, L. B.; Hall, L. H. *J. Comput. Aided Mol. Des*. **1998**, *12*, 557.
9. Tripathi, K. D. *Essentials of Medical Pharmacology*, 4th ed.; Jaypee Brother Medical: New Delhi; 1999; p 184.

10. Rang, H. P.; Dale, M. M.; Ritter, J. M. *Pharmacology* 4th ed; Churchill Livingstone: Edinburgh; 1999; p 139.
11. Lopez-Rodriguez, M. L.; Ayala, D.; Benhamu, B.; Morcillo, M. J.; Viso, A. *Curr. Med. Chem.* **2002**, *9*, 443.
12. Purkayastha, S. K.; Jha, T.; Pal, D. K.; De, A. U. *Anti-cancer Drug Des.* **1993**, *8*, 95.
13. Srikanth, K.; Kumar, C. A.; Goswami, D.; De, A. U.; Jha, T. *Ind. J. Biochem. Biophys.* **2001**, *38*, 120.
14. Srikanth, K.; Debnath, B.; Jha, T. *Bioorg. Med. Chem.* **2002**, *10*, 1841.
15. Srikanth, K.; Debnath, B.; Jha, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 899.
16. Srikanth, K.; Kumar, C. A.; Ghosh, B.; Jha, T. *Bioorg. Med. Chem.* **2002**, *10*, 2119.
17. Debnath, B.; Srikanth, K.; Banerjee, S.; Jha, T. *Internet Electron. J. Mol. Des.* **2002**, *1*, 488.
18. Debnath, B.; Vishnoi, S. P.; Sa, B.; Jha, T. *Internet Electron. J. Mol. Des.* **2003**, *2*, 128.
19. Debnath, B.; Samanta, S.; Roy, K.; Jha, T. *Bioorg. Med. Chem.* **2003**, *11*, 1615.
20. Lopez-Rodriguez, M. L.; Morcillo, M. J.; Fernandez, E.; Rosado, M. L.; Pardo, L.; Schaper, K. J. *J. Med. Chem.* **2001**, *44*, 198.
21. Snedecor, G. W.; Cochran, W. G. *Statistical Methods, 1st ed*; Oxford & IBH: New Delhi, 1967; p 381.
22. Agrawal, V. K.; Khadikar, P. V. *Bioorg. Med. Chem.* **2001**, *9*, 2787.