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QSAR Study on Some Ethenesulfonamide Derivatives as Endothelin Receptor Antagonists

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Abstract

Motivation. QSAR study has been carried out on some ethenesulfonamide derivatives for their ET_A and ET_B receptor antagonism. E–state indices of common atoms and the physicochemical parameters of the substituents were used to find out the essential substitution pattern required for selectivity of this type of compounds towards endothelin receptor.

Method. Correlation Analysis and Multiple Linear Regression (MLR) Analysis have been carried out to derive the best QSAR models.

Results. The best QSAR models obtained separately for endothelin receptor antagonistic activity (pET_BIC_{50} and pET_AIC_{50} as well as log Sel) have correlation coefficients 0.854, 0.820 and 0.864 respectively. These models describe that substitution pattern at phenyl ring (X) is an important contributor to the antagonism of selective endothelin receptor. Hydrophobicity of the *p*–substituents of the phenyl ring (X) has advantageous effect for the selective action on the ET_B receptor. Decrease of molar refractivity of the *p*–substituents and presence of *p*–methyl group in the phenyl ring (X) have advantageous effect to selective ET_A antagonism. Presence of di– or tri–substitution in the phenyl ring (X) further confers selectivity to these compounds.

Conclusions. The study reveals the importance of atom level topological index in identifying atoms and fragments, which are necessary for biological activity.

Keywords. Ethenesulfonamide; endothelin; physicochemical parameters; QSAR; quantitative structure–activity relationships; topological index.

1 INTRODUCTION

Within the last decade many different structural classes of Endothelin (ET) receptor antagonists have been identified [1]. ET receptor plays a fundamental role in many disease processes and the antagonists of this receptor are useful in the treatment of hypertension, coronary artery disease and congestive heart failure especially in combination with other drugs [2–3]. ET–antagonists also have

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analgesic property [2]. Endothelin (ET), the most potent vasoconstrictive endothelium–derived peptide consists of 21 amino acids, exits in three isoforms (ET_1, ET_2 and ET_3) and is acting on two endothelin receptor subtypes (ET_A and ET_B) [4]. ET_A is responsible for mediating vasoconstriction and proliferation of the vascular smooth muscle whereas ET_B mediates vasorelaxation and ET_1 clearance in vascular endothelium [5]. ET_B receptor also mediates some critical processes in the kidney [6]. Thus, selectivity for the ET receptor is an important factor for the efficient treatment of human cardiovascular diseases. Since early endothelin receptor antagonists were peptide in chemical nature as well as cause a non–selective ET_A and ET_B receptor antagonism their clinical potential is often limited [7].

Among the different new chemical classes of ET–antagonists, ethenesulfonamide represents a potent class with varying degrees of ET_A and ET_B antagonistic activity [8–9]. In order to investigate the distinct chemical structural features necessary for the selective ET_B over ET_A antagonism as a part of our composite program of rationale drug design [10–23] a QSAR study was performed using physicochemical parameters of the substituents and electrotopological state atom (E–state) index [18–19,21–26] of the general structure of ethenesulfonamide derivatives (Figure 1).

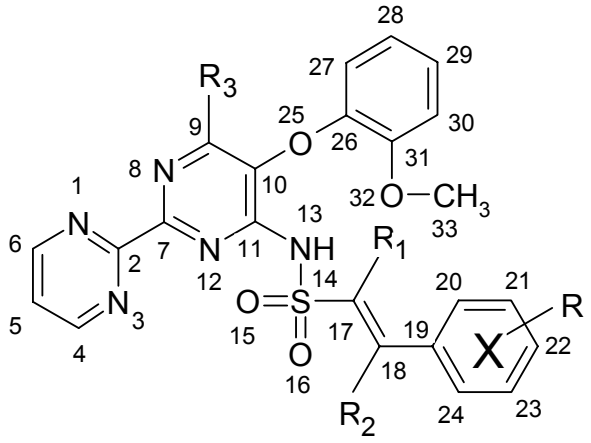

Figure 1. General structure of ethenesulfonamide analogues

2 MATERIALS AND METHODS

2.1 Data Set and Parameters

The general structure of ethenesulfonamide derivatives is shown in Figure 1. The biological activity data were collected from the published work [8] is shown in Table 1. In the QSAR study negative logarithm of ET_B and ET_A receptor antagonistic activity (pET_BIC_{50} and pET_AIC_{50} respectively) as well as logarithm of ET_AIC_{50}/ ET_BIC_{50}, which is expressed as log Sel are considered as dependant parameters to get linear relationship with independent variables. The physicochemical parameters, like molar refractivity (MR), hydrophobicity (π), field effect (F) etc.

of the *p*–substituents of the phenyl ring (X) of Figure 1 were collected from the literature [27]. The E–state indices [18–19,21–26] are atom level topological descriptors encoding the value of electronegativity distributed over an atom according to its bonding degree to non– hydrogen atoms. These indices were calculated as a sum of the intrinsic state value and perturbation effect of the surrounding atoms. These are topological descriptors of structural attribute and information content, which may be correlated well with the biological activity. Besides these, indicator parameters were also used in order to find out the role of the specific substituent at a particular position of the molecule towards the biological activity.

Table 1. ET_A and ET_B antagonistic activities of ethenesulfonamide analogues

No	R	R_1	R_2	R_3	ET_AIC_{50} (nm)	pET_AIC_{50}	ET_BIC_{50} (nm)	pET_BIC_{50}	ET_AIC_{50} / ET_BIC_{50}	log Sel
1	H	H	H	OMe	3.1	–0.491	1200	–3.079	0.003	–2.588
2	H	H	H	$O(CH_2)_2OH$	1.6	–0.204	370	–2.568	0.004	–2.364
3	2–Me	H	H	OMe	1.9	–0.279	320	–2.505	0.006	–2.226
4	3–Me	H	H	$O(CH_2)_2OH$	7.6	–0.881	360	–2.556	0.021	–1.675
5	4–Me	H	H	OMe	2.8	–0.447	190	–2.279	0.015	–1.832
6	2–Cl	H	H	OMe	2.3	–0.362	270	–2.431	0.009	–2.070
7	3–Cl	H	H	OMe	2.2	0.342	770	–2.886	0.003	–2.544
8	4–Cl	H	H	OMe	13	–1.114	280	–2.447	0.046	–1.333
9	4–Et	H	H	OMe	11	–1.041	580	–2.763	0.019	–1.722
10	4–tert–Bu	H	H	OMe	120	–2.079	350	–2.544	0.343	–0.465
11	4–OMe	H	H	OMe	13	–1.114	320	–2.505	0.041	–1.391
12	4–CF_3	H	H	OMe	38	–1.580	350	–2.544	0.109	–0.964
13	4–COOMe	H	H	OMe	12	–1.079	650	–2.813	0.018	–1.734
14	4–COOH	H	H	OMe	140	–2.146	>1000	–3.000	0.140	–0.854
15	2,3–di–Me	H	H	OMe	3.6	–0.556	290	–2.462	0.012	–1.906
16	2,4–di–Me	H	H	OMe	2.2	–0.342	93	–1.968	0.024	–1.626
17	2,5–di–Me	H	H	OMe	37	–1.568	340	–2.531	0.109	–0.963
18	2,6–di–Me	H	H	OMe	8.7	–0.940	74	–1.869	0.118	–0.930
19	2,6–di–Et	H	H	OMe	26	–1.415	180	–2.255	0.144	–0.840
20	2,6–di–Cl	H	H	OMe	4.6	–0.663	160	–2.204	0.029	–1.541
21	2,4,6–tri–Me	H	H	OMe	2.2	–0.342	30	–1.477	0.073	–1.135
22	H	Me	H	OMe	1.6	–0.204	310	–2.491	0.005	–2.287
23	H	Et	H	OMe	3.3	–0.519	790	–2.898	0.004	–2.379
24	H	Pr	H	OMe	170	–2.230	>1000	–3.000	0.170	–0.770
25	H	H	Me	OMe	11	–1.041	760	–2.881	0.014	–1.839
26	2,4,6–tri–Me	Me	H	OMe	6.2	–0.792	130	–2.114	0.048	–1.322

2.2 Calculation of ETSA Indices

E–state indices were calculated using the computer programme 'Mouse' [28] developed in our laboratory. The program was written in C^{++} language and can run in Windows operating system to calculate E–state indices only. Before the calculation the atoms of the molecules were numbered consecutively keeping the serial number of atoms same in all molecules. The intrinsic state (*I*) values of different atoms are given as input and the output file represents the E–state indices (S_i) of common atoms.

2.3 Multiple Regression Analysis

Multiple regression analysis [29–31] was carried out by 'Multi Regress' [32], a program developed in our laboratory. The program written in C^{++} language is able to calculate the coefficients and standard errors of dependant variables as well as deduces parameters like, correlation coefficient (*R*), adjusted R^2 (R^2_A), variance ratio (*F*) and standard error of estimate (*SEE*) etc. These parameters were used to judge the statistical quality of the regression equations. The program also generated the calculated values of biological activity. The final equations had regression coefficients and variance ratio (*F*) significant to more than 95% level as revealed by the student *t*–statistic and *p*–values. Use of more than one variable in the multivariate equation was justified by autocorrelation study with the help of the program.

2.4 Validation of QSAR Models

The predictive powers of the equations were validated by leave–one–out (LOO) cross–validation method [10–23,33], where one compound is deleted at once and prediction of the activity of the deleted compound is made based on the QSAR model. The process is repeated after elimination of another compound until all of the compounds have been deleted at once. For the validation of the models, predicted residual sum of square (*PRESS*), total sum of squares (*SSY*), cross–validated R^2 (R^2_{CV}), standard error of *PRESS* (S_{PRESS}) and predictive standard error or uncertainty factor (*PSE*) for the final equations were considered.

3 RESULTS AND DISCUSSION

For the development of QSAR models, E–state indices of different common atoms and physicochemical parameters like hydrophobicity (π_p) and molar refractivity (MR_p) etc. of the p–substituents of the phenyl ring (X) are used. The values are listed in Table 2. The correlation matrix of independent parameters and biological activities is shown in Table 3. The student *t*–values and associated probability *p*–values of all derived QSAR models are shown in Table 4. Depending on the autocorrelation of various independent parameters, the following mathematical equations were developed in a stepwise fashion for modeling the endothelin receptor (ET_A and ET_B) antagonistic activity by multiple linear regression analysis.

$$pET_BIC_{50} = -2.232(\pm0.243) + 1.119(\pm0.087)\, S_{19} - 0.372(\pm0.169)\, S_{20,24} + 0.244(\pm0.095)\, \pi_p$$
$$N = 26 \quad R = 0.817 \quad R^2 = 0.668 \quad R^2_A = 0.623 \quad F_{(3,22)} = 14.745 \quad p<0.000 \quad SEE = 0.231 \qquad (1)$$
$$PRESS = 1.767 \quad SSY = 3.550 \quad R^2_{CV} = 0.502 \quad S_{PRESS} = 0.283 \quad PSE = 0.261$$

where *N* is the number of data points, *R* is correlation coefficient. R^2_A, *F*, *p*, *SEE*, *PRESS*, *SSY*, R^2_{CV}, S_{PRESS} and *PSE* are adjusted R^2, ratio between the variances of observed and calculated activities, probability factor related to *F*–ratio, standard error of estimate, predicted residual sum of squares, total sum of squares, cross validated R^2, standard error of PRESS and uncertainty factor respectively

[10–23,33]. The values within the parenthesis are confidence intervals of corresponding parameters.

The QSAR Eq. (1) explains up to 66.78% of the variation of the activity data. The presence of E–state indices of atom number 19 (S_{19}) and sum of E–state indices of atom numbers 20, 24 ($S_{20,24}$) in the Eq. (1) imply that substitutions at *o*–positions of the phenyl ring (X) influence the ET_B antagonism and higher value of S_{19} and lower value of $S_{20,24}$ correspond to higher ET_B antagonism. The positive coefficient of S_{19} also suggests that substitution pattern at ethene moiety (atoms 17 and 18) should increase the value of S_{19}. Besides increased hydrophobicity of *p*–substituents confers selective ET_B antagonism as revealed by the positive regression coefficient of π_p in the equation.

Table 2. E–state indices, physicochemical and indicator parameter used in the QSAR study

No	S_{19} [a]	S_{23} [b]	$S_{22,23}$ [c]	$S_{20,24}$ [d]	MR_p [e]	π_p [f]	I_1 [g]	I_2 [g]
1	0.718	1.805	3.644	3.554	0.103	0.000	1.000	0.000
2	0.695	1.791	3.618	3.522	0.103	0.000	1.000	0.000
3	0.764	1.826	3.701	2.749	0.103	0.000	1.000	0.000
4	0.711	1.828	3.737	3.626	0.103	0.000	1.000	0.000
5	0.726	1.888	2.960	3.628	0.565	0.560	0.000	0.000
6	0.530	1.741	3.485	2.089	0.103	0.000	1.000	0.000
7	0.603	1.710	3.397	3.339	0.103	0.000	1.000	0.000
8	0.642	1.653	2.197	3.364	0.603	0.710	1.000	0.000
9	0.737	1.943	3.103	3.690	1.030	1.020	1.000	0.000
10	0.728	1.971	3.121	3.722	1.962	1.980	1.000	0.000
11	0.657	1.721	2.382	3.440	0.787	–0.020	1.000	0.000
12	0.228	0.846	–0.004	2.282	0.502	0.880	1.000	0.000
13	0.534	1.518	1.856	3.150	1.287	–0.010	1.000	0.000
14	0.471	1.362	1.443	2.950	0.693	–0.320	1.000	0.000
15	0.780	1.863	3.821	2.815	0.103	0.000	1.000	1.000
16	0.772	1.908	2.996	2.802	0.565	0.560	0.000	1.000
17	0.780	1.018	2.976	2.839	0.103	0.000	1.000	1.000
18	0.810	1.908	3.820	1.902	0.103	0.000	1.000	1.000
19	0.880	1.984	3.959	2.114	0.103	0.000	1.000	1.000
20	0.341	1.589	3.237	0.582	0.103	0.000	1.000	1.000
.21	0.818	1.991	3.095	1.934	0.565	0.560	0.000	1.000
22	0.735	1.818	3.666	3.596	0.103	0.000	1.000	0.000
23	0.753	1.832	3.690	3.636	0.103	0.000	1.000	0.000
24	0.763	1.843	3.709	3.664	0.103	0.000	1.000	0.000
25	0.764	1.826	3.678	3.628	0.103	0.000	1.000	0.000
26	0.834	2.004	3.111	1.948	0.565	0.560	0.000	1.000

[a] E–state index of atom number 19; [b] E–state index of atom number 23; [c] Sum of E–state indices of atom numbers 22 and 23; [d] Sum of E–state indices of atom numbers 20 and 24; [e] Molar refractivity of *p*–substituents of phenyl ring X; [f] Hydrophobicity of *p*–substituents of phenyl ring X; [g] Indicator parameter

Deletion of the outliers (compound numbers **5**, **11**), might be acting through a different mechanism of action, yielded the Eq. (2).

$$pET_BIC_{50} = -2.194(\pm0.229) + 1.146(\pm0.298)\,S_{19} - 0.401(\pm0.059)\,S_{20,24} + 0.243(\pm0.091)\,\pi_p$$
$$N = 24 \quad R = 0.854 \quad R^2 = 0.729 \quad R^2_A = 0.688 \quad F_{(3,20)} = 17.933 \quad p<0.000 \quad SEE = 0.218 \qquad (2)$$
$$PRESS = 1.476 \quad SSY = 3.498 \quad R^2_{CV} = 0.578 \quad S_{PRESS} = 0.272 \quad PSE = 0.248$$

Eq. (2) explains 72.90% of the activity. The statistical quality of the Eq. (2) is better than that of

Eq. (1) as revealed by the higher F ratio, cross–validated R^2 (R^2_{CV}) and correlation coefficient values.

Table 3. Correlation matrix of the E–state indices, physicochemical and indicator parameters, and biological activity

	S_{19}	S_{23}	$S_{22,23}$	$S_{20,24}$	MR_p	π_p	I_1	I_2	pET_AIC_{50}	pET_BIC_{50}	Log Sel
S_{19}	1.00	0.69	0.71	0.28	–0.11	0.01	–0.30	0.30	0.17	0.23	–0.02
S_{23}		1.00	0.73	0.14	0.04	0.12	–0.32	0.11	0.36	0.27	–0.20
$S_{22,23}$			1.00	0.08	–0.45	–0.26	0.03	0.22	0.41	0.09	–0.36
$S_{20,24}$				1.00	0.22	0.12	0.20	–0.70	–0.11	–0.62	–0.28
MR_p					1.00	0.74	–0.15	–0.20	–0.41	0.01	0.42
π_p						1.00	–0.28	–0.05	–0.24	0.22	0.38
I_1							1.00	–0.41	–0.31	–0.63	–0.08
I_2								1.00	0.10	0.71	0.34
pET_AIC_{50}									1.00	0.32	–0.81
pET_BIC_{50}										1.00	0.30
Log Sel											1.00

Table 4. *t*–statistics and *p*–values of QSAR equations

Eq.	Intercept/Parameters	t–value	p–value	Eq.	Intercept/Parameters	t–value	p–value
(1)	Intercept	–9.200	0.000	(3)	Intercept	–2.355	0.029
	S_{19}	3.536	0.002		$S_{22,23}$	2.673	0.015
	$S_{20,24}$	–6.112	0.000		MR_p	–3.567	0.002
	π_p	2.554	0.018		I_1	–2.535	0.020
(2)	Intercept	–9.574	0.000	(4)	S_{23}	–3.759	0.001
	S_{19}	3.840	0.001		MR_p	6.246	0.000
	$S_{20,24}$	–6.823	0.000		I_2	4.073	0.001
	π_p	2.668	0.015				

Similarly regression equation is developed for the ET_A antagonistic activity. Since the resultant equation for the ET_A antagonistic activity using all compounds showed poor correlation, deletion of compounds were tried and after deletions of compound numbers **17**, **19** and **24** the model obtained for ET_A antagonism is as follows:

$$pET_AIC_{50} = -0.844(\pm0.359) + 0.231(\pm0.087)\, S_{22,23} - 0.601(\pm0.169)\, MR_p - 0.476(\pm0.188)\, I_1$$
$$N = 23 \quad R = 0.820 \quad R^2 = 0.672 \quad R^2_A = 0.621 \quad F_{(3,19)} = 13.006 \quad p<0.000 \qquad (3)$$
$$SEE = 0.339 \quad PRESS = 3.673 \quad SSY = 6.653 \quad R^2_{CV} = 0.448 \quad S_{PRESS} = 0.440 \quad PSE = 0.400$$

where the indicator parameter I_1 represents the absence of methyl group at *p*–position of the phenyl ring (X). The presence of composite E–state index $S_{22,23}$ (sum of E–state indices of atom numbers 22, 23) in Eq. (3) clearly demonstrate that atom no 22 and 23 are important for the ET_A antagonistic activity and higher value of $S_{22,23}$ is conducive to the desired activity. The *p*–substituents should be of low bulk or of lower molar refractivity (MR_p) value and especially methyl substituent has a favorable effect on ET_A receptor antagonism.

Attempt was done to derive QSAR model taking into account the logarithm of ET_AIC_{50}/ ET_BIC_{50} expressed as log Sel as a dependant variable to further explore the selective binding of

ethenesulfonamide derivatives to ET_B receptor. The combination of S_{23} (E–state index of atom number 23), MR_p (molar refractivity of the p–substituents of the phenyl ring) and another indicator parameter I_2 for the presence of di– or tri–substitution at the phenyl ring gave the QSAR Eq. (4). However, the intercept of this equation is not significant at 95% level. Omitting the intercept, the Eq. (4) is expressed as:

$$\begin{gathered}\log \text{Sel} = -0.904(\pm 0.240)\, S_{23} + 0.988(\pm 0.158)\, MR_p + 0.605(\pm 0.149)\, I_2 \\ N = 23 \quad R = 0.864 \quad R^2 = 0.746 \quad R^2_A = 0.706 \quad F_{(3,19)} = 18.618 \quad p<0.000 \\ SEE = 0.323 \quad PRESS = 2.687 \quad SSY = 7.827 \quad R^2_{CV} = 0.657 \quad S_{PRESS} = 0.376 \quad PSE = 0.342\end{gathered} \tag{4}$$

The explained variance of the Eq. (4) is 74.60%. The compounds numbers **13**, **19** and **24** were considered as outliers to derive the above model. Lower value of S_{23} (E-state index of atom 23) and higher value of MR_p are conducive to selective ET_B receptor binding. Moreover, presence of di– or tri–substitution at the phenyl ring of ethenesulfonamide derivatives may increase its selectivity towards ET_B receptor binding. A plot of observed versus calculated log Sel activities is shown in Figure 2.

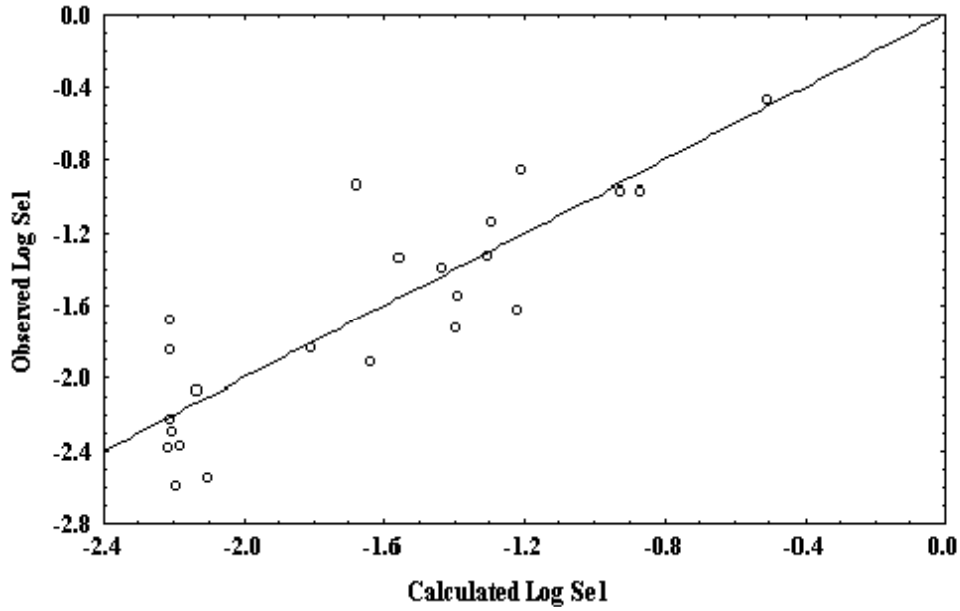

Figure 2. Observed log Sel versus calculated log Sel activity for the ethenesulfonamide derivatives.

The predictive power of the final Eqs. (2), (3) and (4) were evaluated by the Leave–One–Out cross–validation (LOO) method. The predictive variance of the QSAR Eqs. (2), (3) and (4) are 68.80%, 62.10% and 74.60% respectively. Among these final models the QSAR model (4) is more predictive which is evidenced from its higher R^2_{CV} value. The Observed (Obs), calculated (Calc), residual (Res), LOO–predicted (Pred) and predicted residual (Pres) values of activities of Eqs. (2) and (3) as well as Eq. (4) are shown in Table 5 and Table (6) respectively.

Table 5. Observed (Obs), calculated (Calc), residual (Res), LOO (Pred) and predicted residual (Pres) of Eqs. (2) and (3)

No	Eq. (2) (pET_BIC_{50})					Eq. (3) (pET_AIC_{50})				
	Obs	Calc	Res	Pred	Pres	Obs	Calc	Res	Pred	Pres
1	–3.079	–2.796	–0.283	–2.769	–0.310	–0.491	–0.539	0.048	0.544	0.053
2	–2.568	–2.809	0.241	–2.831	0.263	–0.204	–0.545	0.341	0.575	0.371
3	–2.505	–2.420	–0.085	–2.414	–0.091	–0.279	–0.526	0.247	0.549	0.270
4	–2.556	–2.833	0.277	–2.861	0.305	–0.881	–0.518	–0.363	0.484	–0.397
5	–2.279	–	–	–	–	–0.447	–0.499	0.052	0.517	0.070
6	–2.431	–2.424	–0.007	–2.423	–0.008	–0.362	–0.576	0.214	0.594	0.232
7	–2.886	–2.841	–0.045	–2.837	–0.049	0.342	–0.596	0.254	0.617	0.275
8	–2.447	–2.634	0.187	–2.654	0.207	–1.114	–1.175	0.061	1.181	0.067
9	–2.763	–2.581	–0.182	–2.543	–0.220	–1.041	–1.222	0.181	1.253	0.212
10	–2.544	–2.371	–0.173	–2.137	–0.407	–2.079	–1.778	–0.300	1.212	–0.867
11	–2.505	–	–	–	–	–1.114	–1.243	0.129	1.255	0.141
12	–2.544	–2.634	0.090	–2.713	0.169	–1.580	–1.623	0.043	1.697	0.117
13	–2.813	–2.847	0.034	–2.851	0.038	–1.079	–1.665	0.586	1.826	0.747
14	–3.000	–2.914	–0.086	–2.894	–0.106	–2.146	–1.403	–0.743	1.231	–0.915
15	–2.462	–2.428	–0.034	–2.426	–0.036	–0.556	–0.498	–0.058	0.493	–0.063
16	–1.968	–2.296	0.328	–2.324	0.356	–0.342	–0.491	0.149	0.541	0.199
17	–2.531	–2.438	–0.093	–2.431	–0.100	–1.568	–	–	–	–
18	–1.869	–2.028	0.159	–2.061	0.192	–0.940	–0.499	–0.441	0.454	–0.486
19	–2.255	–2.033	–0.222	–1.979	–0.276	–1.415	–	–	–	–
20	–2.204	–2.036	–0.168	–1.880	–0.324	–0.663	–0.633	–.029	0.631	–0.032
21	–1.477	–1.896	0.419	–1.999	0.522	–0.342	–0.468	.126	0.510	0.168
22	–2.491	–2.793	0.302	–2.823	0.332	–0.204	–0.534	.330	0.564	0.360
23	–2.898	–2.788	–0.109	–2.777	–0.121	–0.519	–0.529	.010	0.529	0.011
24	–3.000	–2.788	–0.212	–2.765	–0.235	–2.230	–	–	–	–
25	–2.881	–2.773	–0.108	–2.761	–0.120	–1.041	–0.531	–0.510	0.485	–0.556
26	–2.114	–1.883	–0.231	–1.822	–0.292	–0.792	–0.464	–0.327	0.355	–0.437

Table 6. Observed (Obs), calculated (Calc), residual (Res), LOO (Pred) and predicted residual (Pres) values of Eq. (4)

No	Obs	Calc	Res	Pred	Pres
1	–2.588	–2.193	–0.395	–2.150	–0.438
2	–2.364	–2.180	–0.184	–2.161	–0.203
3	–2.226	–2.212	–0.0148	–2.210	–0.016
4	–1.675	–2.213	0.538	–2.273	0.598
5	–1.832	–1.811	–0.020	–1.809	–0.022
6	–2.070	–2.135	0.065	–2.141	0.072
7	–2.544	–2.107	–0.437	–2.064	–0.480
8	–1.333	–1.561	0.228	–1.579	0.246
9	–1.722	–1.402	–0.321	–1.342	–0.380
10	–0.465	–0.506	0.041	–0.569	0.105
11	–1.391	–1.441	0.050	–1.446	0.055
12	–0.964	–0.932	–0.033	–0.900	–0.064
13	–1.734	–	–	–	–
14	–0.854	–1.209	0.355	–1.277	0.423
15	–1.906	–1.640	–0.266	–1.589	–0.317
16	–1.626	–1.224	–0.402	–1.143	–0.483
17	–0.963	–0.876	–0.087	–0.809	–0.154
18	–0.930	–1.681	0.751	–1.833	0.903
19	–0.840	–	–	–	–
20	–1.541	–1.392	–0.149	–1.363	–0.178
21	–1.135	–1.299	0.164	–1.336	0.201
22	–2.287	–2.204	–0.083	–2.195	–0.092
23	–2.379	–2.217	–0.162	–2.199	–0.180
24	–0.770	–	–	–	–
25	–1.839	–2.212	0.372	–2.253	0.413
26	–1.322	–1.311	–0.011	–1.308	–0.013

4 CONCLUSIONS

The three final QSAR models [Eqs. (2) and (3) as well as Eq. (4)] reveal essential substitutional requirements and the potentiality of E–state index to determine the atoms/fragments necessary for selective action on ET_B receptor as shown in Figure 3. The QSAR models clearly explain that phenyl moiety (X) of ethenesulfonamide has important contribution to the selective antagonism of ET_A/ET_B receptor. In the phenyl ring (X) the atom numbers 19, 20 and 24 are important for ET_B antagonism and hydrophobicity of the *p*–substituents has advantageous effect for the selective action on the ET_B receptor. On the other hand, the atom numbers 22 and 23 have major influence on the selective ET_A antagonism. Besides increase of molar refractivity of the *p*–substituents and absence of *p*–methyl group in the phenyl ring (X) have advantageous effect to selective ET_B antagonism. Moreover, presence of di– or tri–substitution at the phenyl ring (X) further improves its selectivity towards ET_B receptor. Thus, this study may be helpful for further synthesis of this type of compounds to increase the selectivity for ET_B over ET_A receptor by changing the substituent pattern at the phenyl ring (X).

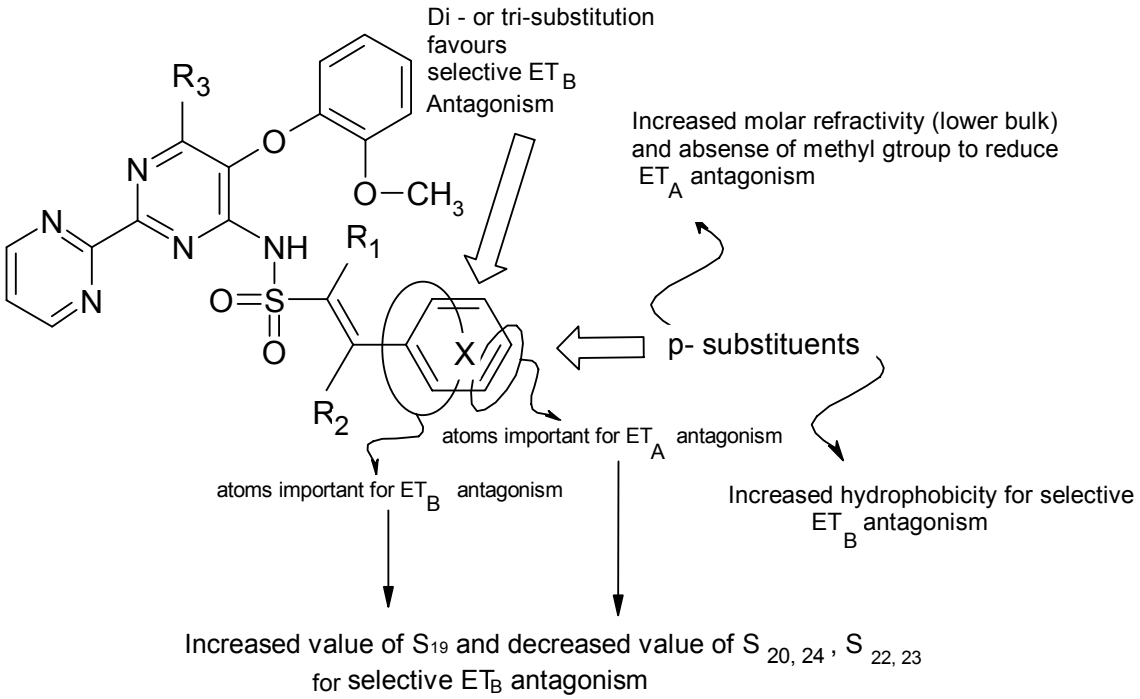

Figure 3. Required structural features for ET_B over ET_A selective antagonism of ethenesulfonamide analogues.

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5 REFERENCES

[1] C. Boss, M. Bolli and T. Weller, Endothelin receptor antagonists: structures, synthesis, selectivity and therapeutic applications, *Curr. Med. Chem.* **2002**, *9*, 349–383.
[2] R. R. Wenzel, P. Czyborra, T. Luscher and T. Philipp, Endothelin in cardiovascular control: the role of endothelin antagonists, *Curr. Hypertens. Rep.* **1999**, *1*, 79–87.
[3] D. Hurlimann, F. Enseleit, G. Noll, T. F. Luscher and F. Ruschitzka, Endothelin antagonists and heart failure. *Curr. Hypertense. Rep.* **2002**, *4*, 85–92.
[4] A. Ergul, Endothelin–1 and endothelin receptor antagonists as potential cardiovascular therapeutic agents. *Pharmacotherapy*. **2002**, *22*, 54–65.
[5] E. H. Ohlstein, J. D. Elliott, G. Z. Feuerstein and R. R. Ruffolo, Endothelin receptors: receptor classification, novel receptor antagonists and potential therapeutic targets. *Med. Res. Rev.* **1996**, *16*, 365–390.
[6] P. Nambi, M. Clozel and G. Feuerstein, Endothelin and heart failure. *Heart Fail. Rev.* **2001**, *6*, 335–340.
[7] C. F. van der Walle and D. J. Barlow, Investigations of structural requirements for endothelin antagonism. *Curr. Med. Chem.* **1998**, *5*, 321–335.
[8] H. Harada, J. Kazami, S. Watanuki, R. Tsuzuki, K. Sudoh, A. Fujimori, A. Tanaka, S. Tsukamoto and I. Yanagisawa, Ethenesulfonamide derivatives, a novel class of orally active endothelin–A receptor antagonists. *Chem. Pharm. Bull.* **2001**, *49*, 606–612.
[9] H. Harada, J. Kazami, S. Watanuki, R. Tsuzuki, K. Sudoh, A. Fujimori, M. Sanagi, M. Orita, H. Nakahara, J. Shimaya, S. Tsukamoto, A. Tanaka and I. Yanagisawa, Ethenesulfonamide and ethanesulfonamide derivatives, a novel class of orally active endothelin–A receptor antagonists. *Bioorg. Med. Chem.* **2001**, *9*, 2955–2968.
[10] S. K. Purkayastha, T. Jha, D. K. Pal and A. U. De, Possible antineoplastic agents part XIII–synthesis, biological evaluation and QSAR studies of some 1–(substituted benzenesulphonyl)–5–oxopyrrolidine–2–carboxylic acid derivatives, *Anticancer Drug Des.* **1993**, *8*, 95–100.
[11] K. Srikanth, C. A. Kumar, D. Goswami, A. U. De and T. Jha, Quantitative structure activity relationship (QSAR) studies of some substituted benzenesulphonyl glutamines as tumor suppressors, *Indian J. Biochem. Biophys.* **2001**, *38*, 120–123.
[12] K. Srikanth, B. Debnath and T. Jha, Synthesis, biological evaluation and QSAR study on antitumor activity of 1,5–*N*, *N'*– distubuted–2–(substituted benzenesulphonyl) glutamamides, *Bioorg. Med. Chem.* **2002**, *10*, 1841–1854.
[13] K. Srikanth, B. Debnath and T. Jha, QSAR study on adenosine kinase inhibition of pyrrolo[2,3–d] pyrimidine nucleoside analogs using Hansch approach, *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 899–902.
[14] K. Srikanth, C. A. Kumar, B. Ghosh and T. Jha, Synthesis, screening and quantitative structure–activity relationship (QSAR) studies on some glutamine analogues for possible anticancer activity, *Bioorg. Med. Chem.* **2002**, *10*, 2119–2131.
[15] B. Debnath, K. Srikanth, S. Banarjee and T. Jha, 1,5–*N*, *N'*–Distibuted–2–(Substituted Benzenesulphonyl)–Glutamamides as Antitumor Agents. Part 2. Synthesis, Biological Activity and QSAR Study, *Internet Electron. J. Mol. Des.* **2002**, *1*, 488–502, http://www.biochempress.com
[16] B. Debnath, S. P. Vishnoi, B. Sa and T. Jha, QSAR study on some dihydrofolate reductase inhibitors, *Internet Electron. J. Mol. Des.* **2003**, *1*, 128–136. http://www.biochempress.com
[17] B. Debnath, S. Samanta, K. Roy and T. Jha, QSAR study on some *p*–arylthio cinnamides as antagonists of biochemical ICAM–1/LFA–1 interaction and ICAM–1/JY–8 cell adhesion in relation to anti–inflammatory activity, *Bioorg. Med. Chem.* **2003**, *11*, 1615–1619.
[18] B. Debnath, S. Gayen, S. K. Naskar, K. Roy and T. Jha, QSAR Study of some Azidopyridinyl Neonicotinoids Insecticides for Their Selective Affinity Towards the Drosophilla Nicoitinic Receptor over Mammalian $\alpha_4\beta_2$ Receptor Using Electrotopological State Atom Index, *Drug Des.Discov.* **2003**, *18*, 81–89.
[19] B. Debnath, S. Samanta, S. K. Naskar, K. Roy and T. Jha, , *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2837–2842.
[20] T. Jha, B. Debnath, S. Samanta and A. U. De, QSAR Study on Some substituted Glutamine analogs As Anticancer Agents. *Internet Electron. J. Mol. Des.* **2003**, *2*, 539–545. http://www.biochempress.com
[21] B. Debnath, S. Gayen, S. Bhattacharya, S. Samanta and T. Jha, QSAR Study on Some Pyridoacridine Ascididemin Analogs as Anti–tumor Agents. *Bioorg. Med. Chem.* **2003**, *11*, 5493–5499.
[22] S. Gayen, B. Debnath, S. Samanta and T. Jha, QSAR study on some anti–HIV HEPT analogues using physicochemical and topological parameters. *Bioorg. Med. Chem.* **2004**, *12*, 1493–1503.
[23] S. Samanta, K. Srikanth, S. Banerjee, B. Debnath, S. Gayen and T. Jha, 5–*N*–Substituted–2–(Substituted Benzenesulphonyl) Glutamines as Antitumor Agents II: Synthesis, Biological Activity and QSAR Study. *Bioorg. Med. Chem.* **2004**, *12*, 1413–1423.
[24] K. Rose, L. H. Hall, and L. B. Kier, Modelling Blood– Brain Barrier Partitioning Using Electrotopological state, *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 651–666.

[25] L. B. Kier and L. H. Hall, An Electrotopological–State Index for atoms in Molecules, *Pharmceutical Res*. **1990**, *7*, 801–807.
[26] C. de Gregorio, L. B. Ksier and L. H. Hall, QSAR modeling with the electrotopological state indices: Corticosteroids, *J*. *Comput*.*–Aid*. *Mol*. *Des*. **1998**, *12*, 557–561.
[27] C. Hansch, A. Leo, *Substitution constants for correlation analysis in chemistry and biology*, Wiley and Sons, New York, 1979.
[28] Mouse: A computer program developed by Naskar SK of the Department of Computer Science and Engineering, Jadavpur University, Kolkata, India and Debnath B one of the authors of this article for the calculation of the ETSA Index.
[29] G. W. Snedecor and W. G. Cochran, *Statistical Methods*, Oxford & IBH, New Delhi, 1967.
[30] D. C. Montgomery (Ed.) *Design and Analysis of experiments*, John Wiley & sons, 1997, New York.
[31] E. J. Lien, Quantitative correlations using Multiple Regression and substitution constants; in: *Drug design*, E. J. Ariens, Academic, 1975, New York.
[32] Multi Regress: A computer program developed by SK Naskar of the Department of Computer Science and Engineering, Jadavpur University, Kolkata, India and B Debnath one of the authors of this article to perform correlation analysis and multiple linear regression analysis.
[33] I. V. Tetko, V. Y. Tanchuk and A. E. Villa, Prediction of n–octanol/water partition coefficients from PHYSPROP database using artificial neural networks and E–state indices. *J*. *Chem*. *Inf*. *Comput*. *Sci*. **2001**, *41*, 1407–1421.