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QSAR Study on Some Antirhino/Enteroviral Vinylacetylene Benzimidazoles [#]

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Abstract

Motivation. A Quantitative Structure–Activity Relationship (QSAR) study on some vinylacetylene benzimidazoles was performed using topological indices and physicochemical parameters to identify and distinguish the pharmacophoric atoms as well as physicochemical properties for their antiviral activity and cellular toxicity tested against human rhinovirus–14 (HRV–14).

Method. Correlation analysis and Multiple Linear Regression (MLR) analysis have been carried out to derive best QSAR models giving important information at atomic/submolecular level.

Results. The present communication shows that the fragment/atoms responsible for the antiviral activity and cellular toxicity of vinylacetylene benzimidazoles are not the same. The substitution pattern at benzimidazole moiety is important for both antiviral activity and cellular toxicity of this type of compounds. By introducing hydrophilic substituents at *p*–position and electronegative substituents at *o*–position of the phenyl ring A it may be possible to increase the selectivity of higher antiviral potency and lower cellular toxicity of vinylacetylene benzimidazoles.

Conclusions. Electrotopological State Atom (ETSA) index is a valuable tool in exploring the pharmacophoric atoms.

Keywords. Vinylacetylene benzimidazoles; antirhino/enteroviral activity; QSAR; ETSA index; pharmacophore.

Abbreviations and notations

ETSA, electrotopological state atom	MLR, multiple linear regression
HRV–14, human rhinovirus–14	QSAR, quantitative structure–activity relationships

1 INTRODUCTION

Vinylacetylene benzimidazole derivatives are the recent addition to antiviral therapy to treat common cold and possess potency and broad spectrum of activity against rhinovirus (110 serotypes) as well as enterovirus (68 serotypes) [1–3]. About 25 years ago, the two compounds Enviroxime and Enviradene [4–5] in benzimidazoles series were reported as antirhino/enteroviral

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agents from Lilly Research Laboratories. But due to the side effect, like emesis in case of Enviroxime and poor peak plasma levels in case of Enviradene [6], a series of Vinylacetylene benzimidazole was made to find an orally bioavailable antiviral drug for the treatment of rhino/enteroviral infections. Some of the compounds of this class have shown good oral bioavailability and antiviral potency.

Vinylacetylene benzimidazoles have the same mechanism of action as Enviroxime [2], revealed by a Cross–sensitivity study with Enviroxime–derived mutants but the detailed mechanism of action of this class remain unclear due to the absence of knowledge of the actual molecular target. However Heinz *et al.* [7] reported that Enviroxime may target the 3A coding region of rhinovirus and poliovirus and it preferentially inhibits synthesis of the viral plus–strand RNA synthesis determined by dot blot analysis of RNA from poliovirus–infected cells. It was also reported that Enviroxime resistance involve two domains within 3A and the amino acid at position 30 is important to determine drug resistance [8].

The present communication is an attempt to quantitatively consider the chemical structural variations required or responsible for the antiviral activity and cellular toxicity of the vinylacetylene benzimidazole derivatives reported by Tebbe *et al.* [3] as a part of our composite program of rational drug design [9–20]. Both physicochemical parameters and electrotopological state atom (ETSA) index [21–25] of some common atoms are used in the Quantitative Structure–Activity Relationship (QSAR) study. Increasing use of this topological index has demonstrated its importance in specifying essential fragments of molecules in QSAR studies. The information generated by this index is focused at the atom level or on the sub–molecular fragments of the molecular skeleton. Thus, it is possible to exploit pharmacophoric atoms for a particular activity in a particular series of molecules by using ETSA indices in the QSAR studies. In the present study, the ability of the indices to shed light on a pharmacophore governing a particular biological activity is illustrated.

2 MATERIALS AND METHODS

The general structure of vinylacetylene benzimidazoles (n = 18) is presented in Figure1 and their observed activities are listed in Table 1. For the development of 2–D QSAR model the average of ETSA indices of different common atoms and physicochemical parameter like hydrophobicity (π) of the *p*–substituents of the phenyl ring (A) are used. The values are listed in Table 1. The values of the hydrophobicity parameter are taken from reference [21] and ETSA indices [22–25] are calculated by ‘mouse’, a computer program developed in our laboratory. Before the calculation, the

atoms of the molecule are numbered consecutively keeping the serial number of atoms same in all the molecules (Figure 1).

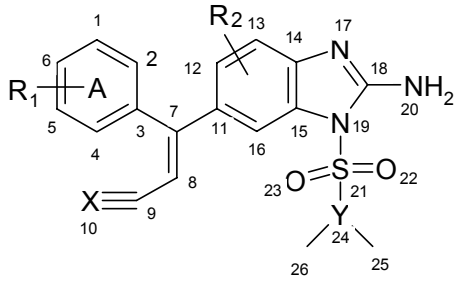

Figure 1. General structure of vinylacetylene benzimidazoles.

Table 1. ETSA indices, hydrophobic parameters and biological activity data of vinylacetylene benzimidazoles.

No	R_1	R_2	X	Y	S_2	S_{av1}	S_{av2}	π_{pA}	IC_{50} (μg/mL)	pIC_{50}	TC_{50} (μg/mL)	pTC_{50}
1	H	H	H	CH	1.948	1.329	2.459	0.000	0.094	1.027	11.000	–1.041
2	3–F	H	H	CH	1.365	1.246	2.380	0.000	0.060	1.222	5.300	–0.724
3	2–F	H	H	CH	–0.428	1.220	2.351	0.000	0.092	1.036	66.000	–1.820
4	4–F	H	H	CH	1.610	1.263	2.398	0.140	0.130	0.886	5.800	–0.763
5	2,5–di F	H	H	CH	–0.661	1.137	2.272	0.000	0.110	0.959	63.000	–1.799
6	3,5–di F	H	H	CH	1.146	1.163	2.300	0.000	0.170	0.770	32.000	–1.505
7	3,4–di F	H	H	CH	1.027	1.181	2.318	0.140	0.190	0.721	19.000	–1.279
8	3–F, 4–OMe	H	H	CH	1.308	1.233	2.373	–0.020	0.061	1.215	5.500	–0.740
9	4–OMe	H	H	CH	1.891	1.316	2.453	–0.020	0.059	1.229	5.200	–0.716
10	4–Me	H	H	CH	1.985	1.333	2.468	0.560	0.075	1.125	5.700	–0.756
11	4–NMe_2	H	H	CH	1.985	1.333	2.473	0.180	0.117	0.932	5.300	–0.724
12	3–CF_3	H	H	CH	0.990	1.135	2.281	0.000	0.400	0.398	>100.000	–
13	4–OCF_3	H	H	CH	1.421	1.182	2.330	1.040	0.550	0.260	18.000	–1.255
14	3–Cl	H	H	CH	1.797	1.303	2.438	0.000	0.210	0.678	20.000	–1.301
15	H	5–F	H	CH	1.795	0.850	2.268	0.000	1.500	–0.176	13.000	–1.114
16	H	7–F	H	CH	1.795	0.804	2.082	0.000	2.800	–0.447	57.000	–1.756
17	5–F	H	H	N	1.721	1.202	2.535	0.000	0.061	1.215	>100.000	–
18	5–F	H	CH_3	CH	1.771	1.275	2.442	0.000	0.260	0.585	3.100	–0.491

ETSA index is an important tool to uncover a functional region of molecule with potential as a pharmacophore [26]. In E–state formalism an initial consideration was taken that every atom in a molecule is different from other atoms in the molecule except where atoms mapped on to each other through a symmetry operation, due to the difference in electronic and topological environment. The E–state index (S_i) of an atom (i) in a molecule is composed of an intrinsic state (I_i) and the perturbation effect (Δ_{ij}). The general expression of the intrinsic state value of atom (i) in N row of the periodic table is given as:

$$I_i = [((2/N)^2\delta^v + 1)/ \delta] \quad (1)$$

where δ^v = number of valence electron – number of hydrogen atom attached, and δ = number of sigma electron – number of hydrogen atom attached.

The information encoded into the atom intrinsic value is of both electronic and topological. The

count of π and lone pair electrons (δ^v) gives important electronic information because electrons occupying these orbitals are more reactive and closely associated with long–range non–covalent intermolecular interaction such as drug–receptor encounters. The important topological attribute is the relative degree of mantle atom or buried atom status, encoded by the number of skeletal neighbours (δ). The general expression for the perturbation effect as follows:

$$\Delta_{ij} = \Sigma(I_i - I_j) / r_{ij}^2 \quad (2)$$

where r_{ij} is the topological distance in the shortest path between the atoms, given as the number *i* and *j*. Thus, the ETSA index, derived from both the electronic and topological structure information from all other atoms within the structure, is calculated as

$$S_i = I_i + \Delta_{ij} \quad (3)$$

In the QSAR study negative of logarithmic scale of antiviral activity (pIC_{50}) and cellular toxicity (pTC_{50}) against human rhinovirus–14 (HRV–14) were considered as dependent parameters. Regression analysis is done using software 'Statistica'. Correlation analysis of ETSA indices and physicochemical parameters were carried out. The auto–correlated parameters were eliminated stepwise through a careful observation. All possible combinations of parameters were considered. The statistical quality of the regression equations were characterized by the following statistical parameters: correlation coefficient (*R*), percentage of explained variance (%*EV*), adjusted R^2 (R^2_A), variance ratio (*F*), standard error of estimate (*SEE*). All the final equations have regression coefficients, intercepts and variance ratio (*F*) significant to more than 95% level. Use of more than one variable in the multivariate equation was justified by autocorrelation study. The predictive powers of the equation are validated by Leave–one–out (LOO–) cross validation method [27]. 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 are considered for the validation of the models.

3 RESULTS AND DISCUSSION

The E–state indices were calculated for each common atom in the set and attempt was done to regress [28–30] individually and in multiples against the pIC_{50} and pTC_{50} values for the 18 vinylacetylene benzimidazoles.

From the autocorrelation study, it was found that ETSA indices of atom no 11–21 have higher individual correlation to pIC_{50} values and they were highly auto–correlated, and cannot be used together in a single QSAR model. It is obvious that QSAR model using one of these ETSA indices may loose some information regarding the pharmacophoric requirements for the

antirhino/enteroviral activity. To accommodate these ETSA indices in a single QSAR equation as an independent parameter, an average (S_{av1}) of these was taken and the resultant model yielded statistical information as follows:

$$\begin{gathered} \mathrm{pIC_{50}} = -2.447\ (\pm 0.546) + 2.682\ (\pm 0.454)\ S_{av1} \\ n = 18 \quad R = 0.828 \quad \%EV = 68.598 \quad R^2_A = 0.666 \quad F_{(1,16)} = 34.953 \quad p<0.001 \quad SEE = 0.279 \\ PRESS = 1.485 \quad SSY = 2.980 \quad R^2_{CV} = 0.502 \quad S_{PRESS} = 0.315 \quad PSE = 0.287 \end{gathered} \tag{4}$$

where n is the number of data points, R is correlation coefficient. $\%EV$, R^2_A, F, p, SEE, $PRESS$, SSY, R^2_{CV}, S_{PRESS}, PSE are percentage of explained variance, 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 and standard error of $PRESS$ respectively. Quantities in parenthesis are the corresponding standard deviations of the coefficients.

The physicochemical parameters like electronic, molar refractivity, hydrophobicity (π_{pA}) were taken for the *p*–substituents of phenyl ring A in vinylacetylene benzimidazole and attempt was made whether they can be used along with S_{av1}. It was found that only hydrophobicity parameter could be used along with S_{av1} and yielded the model (5):

$$\begin{gathered} \mathrm{pIC_{50}} = -2.528\ (\pm 0.509) + 2.791\ (\pm 0.426)\ S_{av1} - 0.441\ (\pm 0.235)\ \pi_{pA} \\ n = 18 \quad R = 0.864 \quad \%EV = 74.582 \quad R^2_A = 0.712 \quad F_{(2,15)} = 22.007 \quad p<0.001 \quad SEE = 0.259 \\ PRESS = 1.328 \quad SSY = 2.980 \quad R^2_{CV} = 0.554 \quad S_{PRESS} = 0.298 \quad PSE = 0.272 \end{gathered} \tag{5}$$

Two distinct chemicals with larger residual (compounds **18** and **14**) where the acetylene moiety is methyl substituted and *m*–Cl substituent in the phenyl ring A respectively may act indirectly or through a different mechanism of action, may behave as outliers. The QSAR model from Eq. (5) fails to correlate these structural features of these two compounds with their antiviral activities. After deleting the compounds **14**, **18** the final QSAR model is as follows:

$$\begin{gathered} \mathrm{pIC_{50}} = -2.813\ (\pm 0.406) + 3.092\ (\pm 0.344)\ S_{av1} - 0.562\ (\pm 0.187)\ \pi_{pA} \\ n = 16 \quad \mathrm{DC} = \mathbf{14},\mathbf{18} \quad R = 0.930 \quad \%EV = 86.44 \quad R^2_A = 0.844 \quad F_{(2,13)} = 41.448 \quad p<0.001 \\ SEE = 0.202 \quad PRESS = 0.698 \quad SSY = 3.926 \quad R^2_{CV} = 0.822 \quad S_{PRESS} = 0.232 \quad PSE = 0.209 \end{gathered} \tag{6}$$

where DC refers to the deleted compounds behaves as outliers. It is clearly revealed that deletions of outliers significantly improve the statistical quality of QSAR model from Eq. (5), where the correlation coefficient (R) increases by about 0.7 units. The predictive power of Eq. (6) is good as the cross–validated R^2 value >0.7. The model explains up to 86.44% of the variation of the antiviral activity. The equation gives lower values of $PRESS$, S_{PRESS}, which ensure that optimum number of variables are taken and there is no over prediction in the model. The equation model reveals that benzimidazole moiety along with atom no 20 and 21 is strong contributor to the antiviral activity of

these type of compounds. The equation clearly suggests that higher value of S_{av1} corresponds to higher antiviral activity as evidenced by the positive regression coefficient in the equation.

Another important feature in the equation model is the relationship of antiviral activity to the hydrophobicity parameter π_{pA}. The negative regression coefficient in the equation clearly demonstrates that increase of hydrophobicity of the *p*–substitution of the phenyl ring A has detrimental effect to the activity. So lower hydrophobic rather hydrophilic substitutions at this position is preferable for the antiviral activity. The ETSA index S_{av1} carries the electronic and topological informations of the substituent pattern of the benzimidazole moiety for the antiviral activity. Thus substituent pattern in the benzimidazole moiety should be such that will increase the value of S_{av1}. More electronegative substituents such as fluorine in the benzimidazole moiety are destructive to the antiviral activity. These relationships between substitution patterns on benzimidazole moiety suggest the possibility of a pharmacophore feature associated with the moiety.

When the ETSA indices and the physicochemical parameters were correlated with the pTC_{50} (negative logarithm of TC_{50} against HRV–14) values the ETSA indices of atoms 7–9 and 14–26 are highly auto–correlated and in a similar way a composite ETSA index S_{av2} was formed by taking average of these indices. ETSA index of atom no 2 (S_2) can be used with S_{av2} that yielded the following equation given below.

$$pTC_{50} = -6.988\ (\pm 1.562) + 2.333\ (\pm 0.674)\ S_{av2} + 0.267\ (\pm 0.086)\ S_2$$
$$n = 16 \quad R = 0.840 \quad \%EV = 70.550 \quad R^2_A = 0.660 \quad F_{(2,13)} = 15.571 \quad p<0.001 \quad SEE = 0.255 \qquad (7)$$
$$PRESS = 1.228 \quad SSY = 2.862 \quad R^2_{CV} = 0.571 \quad S_{PRESS} = 0.307 \quad PSE = 0.277$$

After deletion of the compound **14** (DC = **14**), which may act in a different mechanism and considered as an outlier as discussed previously in case of Eq. (6), the final equation obtained as follows:

$$pTC_{50} = -7.493\ (\pm 1.371) + 2.552\ (\pm 0.592)\ S_{av2} + 0.283\ (\pm 0.075)\ S_2$$
$$n = 15 \quad \text{DC} = \mathbf{14} \quad R = 0.891 \quad \%EV = 79.341 \quad R^2_A = 0.759 \quad F_{(2,12)} = 23.043 \quad p<0.001 \qquad (8)$$
$$SEE = 0.220 \quad PRESS = 0.899 \quad SSY = 2.824 \quad R^2_{CV} = 0.682 \quad S_{PRESS} = 0.274 \quad PSE = 0.245$$

The resultant Eq. (8) is considered to be the best model in case of pTC_{50}, which explains 79.341% of the variation of the biological activity data. The atoms associated with S_{av2} and S_2 constitute the potential region for the cellular toxicity. The equation clearly explains that lower cellular toxicity corresponds to lower value of S_2 and S_{av2} indices as evidenced by the positive regression coefficients.

Table 2. Correlation matrices for the final Eqs. (6) and (8)

Eqn (6)	π_{pA}	S_{av1}	pIC_{50}	Eqn (8)	S_2	S_{av2}	pTC_{50}
π_{pA}	1.00	0.18	–.15	S_2	1.00	0.29	0.69
S_{av1}		1.00	0.88	S_{av2}		1.00	0.74
pIC_{50}			1.00	pTC_{50}			1.00

The final Eqs. (6) and (8) obtained are considered statistically significant because the associated probability values < 0.05 and therefore variance ratio (F) is statistically significant. The use of more than one variable in the multivariate equations was justified by the autocorrelation study. The correlation matrices for the final Eqs. (6) and (8) are presented in Table 2. The student t–values and probability–p values of all the equations are given in Table 3.

Table 3. *t*– and *p*– values of all QSAR equations

Eq no	Intercept/Parameter	*t*–value	*p*–value	Eq no	Intercept/Parameter	*t*–value	*p*–value
(4)	Intercept	–4.482	<0.001	(7)	Intercept	–4.472	<0.001
	S_{av1}	5.912	<0.001		S_2	3.100	<0.008
					S_{av2}	3.460	<0.004
(5)	Intercept	–4.965	<0.001				
	π_{pA}	–1.879	<0.080	(8)	Intercept	–5.468	<0.001
	S_{av1}	6.560	<0.000		S_2	3.776	<0.003
					S_{av2}	4.315	<0.001
(6)	Intercept	–6.923	<0.001				
	π_{pA}	–3.010	<0.010				
	S_{av1}	8.992	<0.001				

Table 4. Observed (Obs), calculated (Calc), residual (Res), LOO–predicted (Pred), and predicted residual (Pres) values of Eqs. (6) and (8)

Cpd	Obs pIC_{50}	Obs pTC_{50}	Eq. (6)				Eq. (8)			
			Calc	Res	Pred	Pres	Calc	Res	Pred	Pres
1	1.027	–1.041	1.295	–0.268	1.341	–0.314	–0.665	–0.376	–0.597	–0.440
2	1.222	–0.724	1.039	0.183	1.020	0.202	–1.033	0.309	–1.056	0.332
3	1.036	–1.820	0.958	0.078	0.951	0.084	–1.612	–0.207	–1.464	–0.356
4	0.886	–0.763	1.015	–0.129	1.026	–0.140	–0.918	0.155	–0.931	0.168
5	0.959	–1.799	0.702	0.257	0.680	0.279	–1.881	0.082	–1.960	0.161
6	0.770	–1.505	0.783	–0.013	0.784	–0.014	–1.298	–0.207	–1.278	–0.227
7	0.721	–1.279	0.758	–0.037	0.761	–0.040	–1.285	0.007	–1.286	0.007
8	1.215	–0.740	1.009	0.205	0.989	0.226	–1.066	0.325	–1.089	0.349
9	1.229	–0.716	1.266	–0.037	1.273	–0.044	–0.697	–0.019	–0.694	–0.022
10	1.125	–0.756	0.995	0.130	0.951	0.174	–0.634	–0.122	–0.609	–0.147
11	0.932	–0.724	1.207	–0.275	1.246	–0.314	–0.619	–0.105	–0.598	–0.126
12	0.398	–	0.696	–0.298	0.722	–0.324	–	–	–	–
13	0.260	–1.255	0.257	0.003	0.247	0.013	–1.145	–0.110	–1.136	–0.118
14	0.678	–1.301	–	–	–	–	–	–	–	–
15	–0.176	–1.114	–0.185	0.009	–0.190	0.014	–1.197	0.083	–1.214	0.100
16	–0.447	–1.756	–0.327	–0.120	–0.223	–0.224	–1.672	–0.084	–1.469	–0.287
17	1.215	–	0.903	–0.311	0.877	0.338	–	–	–	–
18	0.585	–0.491	–	–	–	–	–0.759	0.268	–0.796	0.305

The predictive power of the equations were confirmed by LOO–cross–validation method, 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. The observed (Obs), calculated (Calc), LOO–predicted (Pred) and predicted residual (Pres) values of the two final Eqs. (6) and (8) are shown in Table 4.

4 CONCLUSIONS

The present study illustrates the ability of ETSA indices to identify a functional region of a molecule with potential as a pharmacophore for a particular activity. The two final statistically robust QSAR models (Eqs. (6) and (8)) contain composite ETSA indices S_{av1} and S_{av2} respectively, clearly demonstrate that the atoms associated with these indices may form the possible pharmacophore moiety inherent in a set of closely related structures for the desired activity. The pharmacophoric atoms in the vinylacetylene benzimidazoles for the antiviral activity and the cellular toxicity against HRV–14 are presented in Figure 2.

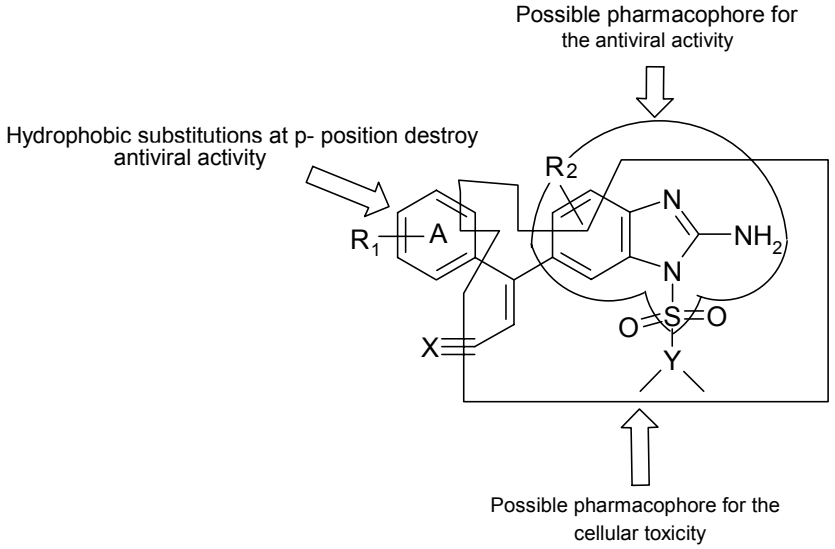

Figure 2. Possible pharmacophore for the antiviral activity and cellular toxicity of vinylacetylene benzimidazoles.

An important feature which is also revealed, is that by changing the substitution pattern at the phenyl ring A in vinylacetylene benzimidazole derivatives, it may be possible to produce better active compounds having lower cellular toxicity. This selectivity of higher antiviral potency and lower toxicity may be possible by introducing hydrophilic substitutions at *p*–position of the ring and substitutions capable to lower the value of ETSA index of atom no 2 (S_2) at o–position of the ring. The substitutions, able to increase the value of S_{av1} and decrease the value of S_{av2} at the remaining part of the vinylacetylene benzimidazole structure confer further this type of selectivity. This useful

information encoded by the final QSAR models may be communicated to synthetic chemists for the development of biologically safe new compound having the potential antiviral activity to treat rhino/enteroviral infections.

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