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An Insight into the Structural Requirement Qsar Approach on Substituted Isoxazolidines Derivatives as Angiotensin II Receptor Antagonist

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Abstract: Quantitative structure activity relationship (QSAR) studies of thirteen quinazolinone Isoxazolidines derivatives were performed for their Angiotensin II receptor antagonist's activity using VlifeMDS3.5 software. Multiple regression analysis (MLR) coupled with stepwise variable selection method was applied to derive QSAR models which were further validated for statistical significance and predictive ability by internal and external validation. The best QSAR model was selected, having correlation coefficient r^2 = 0.8207 and cross validated squared correlation coefficient q^2 = 0.7186 with external predictive ability of pred_r^2 = 0.7851 coefficient of correlation of predicted data set (pred_r^2se) 0.4206 and degree of freedom 26. The results obtained from QSAR studies could be used in designing better Ang II activity among the congeners in future.

Key words: Angiotensin II · Isoxazolidines · QSAR · VlifeMDS3.5

INTRODUCTION

The renin-angiotensin system (RAS) plays an important role in blood pressure regulation and electrolyte homeostasis [1]. Angiotensin II (AII) is the biologically active component of the RAS and is responsible for most of the peripheral effects of this system. The octapeptide angiotensin II (Ang II) is produced by the renin angiotensin system (RAS) and is a potent vasoconstrictor and thus plays an important role in the pathophysiology of hypertension [2]. This directed many researchers toward the designing of drugs to block the effect of Ang II either by inhibiting the angiotensin converting enzyme (ACE) or renin or by blocking the Ang II receptor [3]. Renin, an enzyme produced primarily by the juxtaglomerular cells of the kidney, catalyzes the conversion of angiotensinogen into an inactive substance, angiotensin I (A-I). Angiotensin-converting enzyme (ACE) then converts Ang -I to the physiologically active angiotensin II (Ang-II), which causes potent vasoconstriction, aldosterone secretion and sympathetic activation. All of these actions contribute to the development of hypertension [4-5]. Quantitative structure activity relationship (QSAR) is one of the major tools in drug discovery to explore ligand-receptor/enzyme interactions, especially when either the structural details of the target are not known or protein binding data of ligand is unavailable. 2D-QSAR does not involves complex alignment or assumptions on conformations, therefore they can easily be applied to large compound sets, both in model building and in model application to new compounds [6]. A number of quantitative structure-activity relationship (QSAR) studies related to design of angiotensin II receptor antagonists drugs have also been reported [7-11]. The present study is aimed to elucidate the structural features of the development of a quantitative structure activity relationship with the aid of various physicochemical parameters has been an important task in lead optimization. The relevance of the model for the design of novel derivatives should be assessed not only in terms of predictivity, but also in terms of their ability to provide a chemical and structural explanation of their binding interaction. Here we propose a general model for the antagonist and present minimal structural requirement for an Angiotensin II antagonist.

Experimental

Data for QSAR Studies: The Ang II receptor antagonistic activity data of Substituted quinazolinone were taken from the reported work [12]. The activity data given as IC_{50} values, where IC_{50} refers to the experimentally determined nanomolar concentration of the Isoxazolidines derivatives.

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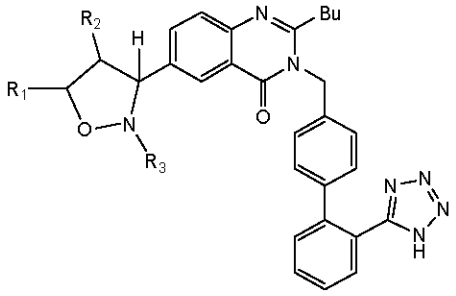
Table 1: Biological activity data and structures of the compounds



Comp.	R_1	R_2	R_3	IC_{50}(nM)	pIC_{50}
1	CH_2OH	H	CH_3	61	1.78533
2	CH_2OH	H	CH_3	43	1.633468
3*	$-(CH_2)_3-$	H	CH_3	98	1.991226
4	$-CH_2\ CH_2CO-$	H	CH_3	42	1.623249
5	$-CH_2\ CH_2CO-$	H	CH_3	98	1.991226
6	$-CH_2\ CH_2CO-$	H	CH_2Ph	79	1.897627
7	$-CH_2OCO-$	H	CH_3	150	2.176091
8*	$-CH_2OCO-$	H	CH_3	68	1.832509
9	$-CH_2OCO-$	H	CH_2Ph	94	1.973128
10	$-CH_2OCO-$	H	CH_2Ph	177	2.247973
11*	$-CH_2CH_2CH_2CO-$	H	CH_3	900	2.954243
12	-1,3-cyclopentyl-	H	CH_3	154	2.187521
13	$-(CH_2)_6-$	H	CH_3	180	2.255273

*test compound

Table 2: 2D QSAR descriptors list required QSAR models

	SaaCHcount	SssssCE-index	SaaNE Index	SsBrE	T_O_Cl_5	T_2_F_1
1	-0.4862	0.084276	0.133537	-0.18126	7	2
2	-0.4736	0.07606	0.128688	-0.15718	7	2
3	-0.4244	0.053352	0.120334	-0.1718	7	2
4	-0.4612	0.059308	0.12082	-0.17729	7	2
5	-0.4637	0.083673	0.132659	-0.17232	7	2
6	-0.4703	0.075009	0.127172	-0.17314	7	2
7	-0.4099	0.067817	0.124094	-0.17077	7	1
8	-0.4587	0.071606	0.12562	-0.18129	7	1
9	-0.3268	0.097401	0.136181	-0.14712	3	1
10	-0.3286	0.085895	0.120853	-0.1248	3	1
11	-0.3328	0.085811	0.129659	-0.13865	3	1
12	-0.3252	0.078186	0.121772	-0.13267	3	1
13	-0.2846	0.09665	0.266469	-0.65387	5	3

The biological activity values [IC_{50} (nM)] reported in nanomolar units were converted to their molar units and then further to negative logarithmic scale and subsequently used as the dependent variable for the QSAR analysis. The -log values of IC_{50} (pIC_{50}) along with the structure of the compounds in the series are listed in (Table 1).

Methodology: Various 2D descriptors like element counts, molecular weight, molecular refractivity, log P, topological index, electro-topological index, Baumann alignment independent topological descriptors, etc. were calculated using VLife MDS 3.5; software[13] . The pre-processing of the independent variables (i.e. descriptors) was done by removing invariable (constant column) and cross-correlated descriptors (with r>0.99) which resulted in total 272 descriptors to be used for QSAR analysis. All the structures were constructed using the 2D draw application provided as a tool of main MDS window. The 2D structures were converted to 3D structures by sending them to MDS. Energy minimization and geometry optimization was conducted using Merck Molecular Force Field (MMFF) method with Root Mean Square (RMS) gradient set to 0.01 Kcal/mol A^0 and iteration limit to 10000. Montocarlo conformational search method is similar to the RIPS method that generates a new molecular conformation by randomly perturbing the position of each coordinate of each atom in molecule, followed by energy minimization and optimization is necessary process for proper alignment of molecules around template.

Most stable structure for each compound was generated after energy minimization and used for calculating various physico-chemical descriptors like thermodynamic, steric and electronic. The energy-minimized geometry was used for the calculation of the various 2D descriptors (Individual, Chi, ChiV, Path count, ChiChain, ChiVChain, Chain pathcount, Cluster, Path cluster, Kappa, Element Count, Estate number, Estate contribution, Semi-empirical, Hydophillic-hydophobic, Polar surface area and Alignment independent) and was considered as independent variables in the present study (Table 2). The preprocessing of the independent variables (i.e. descriptors) was done by removing invariable (constant column), which resulted in total 272 descriptors to be used for QSAR analysis.

Model Quality and Validation: This is done to test the internal stability and predictive ability of the QSAR models. Developed QSAR models were validated by the following procedure:

Internal and External Validation: The regression coefficient r^2 is a relative measure of fit by the regression equation. It represents the part of the variation in the observed data that is explained by the regression. Internal validation is carried out using 'leave-one-out' (LOO) method [14].The cross-validated coefficient, q^2, is calculated using the following equation:

$$q^2 = 1 - \frac{\sum (y_i - \hat{y}_i)^2}{\sum (y_i - y_{\text{mean}})^2}$$

Where y_i and y_i are the actual and predicted activity of the i^{th} molecule in the training set, respectively and y_{mean} is the average activity of all molecules in the training set. However, a high q^2 value does not necessarily give a suitable representation of the real predictive power of the model for antimalarial ligands. So, an external validation is also carried out in the present study. The external predictive power of the model is assessed by predicting pIC_{50} value of the three test set molecules, which are not included in the QSAR model development. The predictive ability of the selected model is also confirmed by pred_r^2 or rCVext[2].

$$\text{pred\_r}^2 = 1 - \frac{\sum (y_i - \hat{y}_i)^2}{\sum (y_i - y_{\text{mean}})^2}$$

where y_i and y_i are the actual and predicted activity of the i^{th} molecule in the test set, respectively and y_{mean} is the average activity of all molecules in the training set. The robustness of the selected model is checked by Y - randomization test. The robustness of the models for training sets is examined by comparing these models to those derived for random datasets. Random sets are generated by rearranging the activities of the molecules in the training set. The significance of the models hence obtained is derived based on a calculated Z score[15]. A Z score value is calculated by the following formula:

$$\text{Zscore} = \frac{(h - \mu)}{\sigma}$$

where h is the q^2 value calculated for the actual dataset, ì the average q^2 and ó is its standard deviation calculated for various iterations using models build by different random datasets.

Evaluation of the QSAR Models: The developed QSAR models are evaluated using the following statistical measures: n, (the number of compounds in regression); k, (number of variables); DF, (degree of freedom); optimum component, (number of optimum); r^2 (the squared correlation coefficient), F test (Fischer's value) for statistical significance, q^2 (cross-validated correlation coefficient); pred_r^2, (r^2 for external test set); Z score, (Z score calculated by the randomization test); best_ran_q^2, (highest q^2 value in the randomization test); best_ran_r^2, (highest r^2 value in the randomization test). The regression coefficient r^2 is a relative measure of fit by the regression equation. It represents the part of the variation in the observed data that is explained by the regression. However, a QSAR model is considered to be predictive, if the following conditions are satisfied: $r^2 > 0.6$, $q^2 > 0.6$ and pred_r^2 > 0.5 [16]. The F-test reflects the ratio of the variance explained by the model and the variance due to the error in the regression. High values of the F-test indicate that the model is statistically significant. The low standard error of Pred_r^2se, q^2_se and r^2_se shows absolute quality of fitness of the model.

QSAR by Multiple Linear Regression (MLR) Analysis: Multiple regressions are the standard method for multivariate data analysis. It is also called as ordinary least squares regression (OLS). This method of regression estimates the values of the regression coefficients by applying least squares curve fitting method. For getting reliable results, dataset having typically 5 times as many data points (molecules) as independent variables (descriptors) is required. The regression equation takes the form

$$Y = b1*x1 + b2*x2 + b3*x3 + c$$

Where Y is the dependent variable, the 'b's are regression coefficients for corresponding 'x's (independent variable), 'c' is a regression constant or intercept.

RESULTS AND DISCUSSION

The QSAR study of Substituted Isoxazolidines derivatives through MLR methodology, based on various feature selection methods Using VLife MDS 3.5 software resulted in the following statistically significant models.Molecules with better biological activity compared with the existing Substituted Isoxazolidines derivatives were searched. The general structures of Substituted Isoxazolidines derivatives while the chemical structures, physicochemical parameters and indicator variables are shown in Table 1. A data set of thirteen compounds was divided into training (ten molecules) and test sets (three molecules). Observed, calculated and predicted (leave-one-out, LOO) biological activity data of training set and test set are shown in Tables 3, respectively. QSAR Studies were performed using VLife Molecular Design Suite software [17-19].

pIC50= -0.7519 (SssNHE-index) + 0.2571 (SsBrE-Index) + 1.824 (T_O_Cl_5) + 0.6836

Optimum components = 3, degree of freedom = 26,n = 13, r^2 = 0.8207, q2 = 0.7186, F test =68.482, r^2 se = 0.5941, q2 se = 0.1852, pred_r^2 = 0.7851, pred_r2se = 0.4206

Model - 1 developed has a correlation coefficient (r2) of 0.8207, significant cross validated correlation coefficient (q2) of 0.7186, F test of 68.482, shows the overall statistical significance level to be 99.99 % of the model, which means that the probability of failure for model is 1 in 10,000. r2 for external test set (pred_r2) 0.7851, coefficient of correlation of predicted data set (pred_r2se) 0.4206 and degree of freedom 26. The model developed is validated by an external set of compounds with a predictive correlation of coefficient of 0.7851. The model is validated by α_ran_r2 = 0.00131, α_ran_q2 = 0.01, α_ran_pred_r2 = 0.0000, best_ran_r2 = 0.6381, best_ran_q2 = 0.4896, Z score_ran_r2 = 7.473 and Z score_ran_q2 = 3.6300.The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance. The observed and predicted pIC50 along with residual values and Correlation matrix are shown in Table 3 and Table 4. The plot of observed vs. predicted activity is shown in Figure 1. From the plot it can be seen that MLR model is able to predict the activity of training set quite well (all points are close to regression line) as well as external. The major group of descriptors involved sub groups like SssNHE-index, SsBrE-Index and T_O_Cl_5. A high q2 value does not necessarily give a suitable representation of the real predictive power of the model for Ang II ligands. So, an external validation was also carried out in this study. The positive contribution of dipole moment on the biological activity indicated that the increase in SssNHE-index of molecule leads to better Ang II activity.

Table 3: Observed and predicted activities of statistically significant models

Comp.	Observed activity	Predicted Model-1	Predicted Model-2	Predicted Model-3
1	1.78	1.89	1.92	1.69
2	1.63	1.75	1.54	1.79
3	1.99	2.08	1.91	1.86
4	1.62	1.75	1.49	1.55
5	1.99	1.83	2.11	2.06
6	1.89	1.79	1.82	1.98
7	2.17	2.26	2.12	2.08
8	1.83	1.74	1.79	1.94
9	1.97	1.83	2.13	2.04
10	2.24	2.15	2.32	2.41
11	2.95	2.89	3.08	3.19
12	2.18	2.24	2.11	1.97
13	2.25	2.18	2.36	1.75

Table 4: Correlation matrix for QSAR model-1

	pIC50	SssNHE-index	SsBrE-Index	T_O_Cl_5
pIC50	1.000			
SssNHE-index	0.7398	1.000		
SsBrE-Index	0.3276	0.6452	1.000	
T_O_Cl_5	0.4769	0.7214	0.8643	1.000

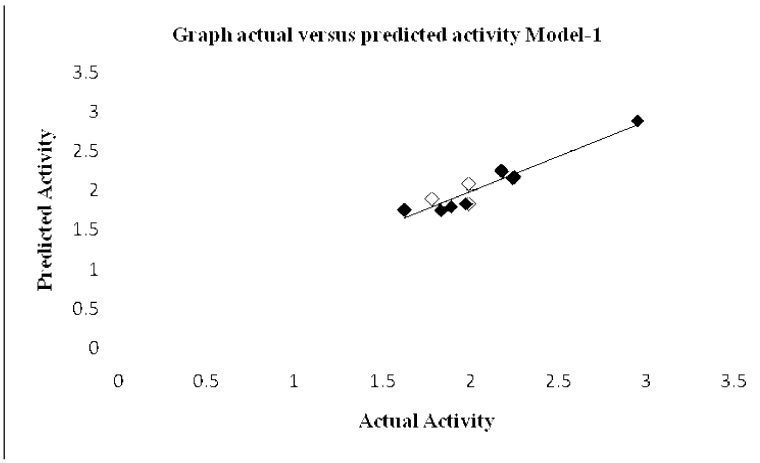


Fig. 1: Plot of actual versus predicted activity for model 1

T_O_Cl_5 are inversely proportional to the activity positive contribution to chlorine increase activity. The careful examination of the descriptors in the model suggests that descriptor T_O_Cl_5, means the count of number of double bonded atoms (single, double or triple bonded) separated from any chlorine atom (single or double bonded) by three bond distance, is directly proportional to the activity and shows that for maximal activity.SssNHE-index describes Electro topological state indices for number of -NH group connected with two single bonds. Its negative contribution in the QSAR model implies that secondary or primary will lead to reduce potency for the Ang II, instead of COOH group.SsBrE-index; this is also an estate contribution descriptor which represents electro topological state indices for number of bromine atoms connect with one single bond. This type of descriptor shows the importance of presence of electron environment on Substituted Isoxazolidines derivatives increase the activity.

pIC_{50} = + 3.683(SsBrE-Index) +0.9836 (SssNHE-index) + 2.8952(T_2_F_1) + 0.3815 (SaaCHcount)+ 0.7522

Optimum components = 3, degree of freedom = 26, n = 13, r^2 = 0.8429, q2 = 0.7816, F test =48.367, r^2 se = 0.6538, q2 se = 0.7546, pred_r^2 = 0.7287, pred_r2se = 0.7681

Model-2 shows 84.29% variance in the observed activity values. The low standard error of r^2_se = 0.6538 demonstrates accuracy of the model. The F test value, 48.367 shows the overall statistical significance level to be 99.99 % of the model, which means that the probability of failure for model is 1 in 10,000. Cross validated q^2 of this model. The model showed an internal predictive power (q^2=0.7816 of 78.16 % and predictivity for external test set (pred_r^2 =0.7287) about 73 %. The positive contribution of SaaCHcount i.e. sum of electro topological state indices for unsubstituted aromatic carbons suggest that the presence of more unsubstituted aromatic carbon will be in favor of higher anti-hypertensive activity. The next most important descriptor which influences the activity variation is SsBrE-Index estate contribution descriptor which represents electro topological state indices for number of bromine atoms connect with one single bond electron environment on Substituted Isoxazolidines derivatives increase the activity. SssNHE-index describes Electro topological state indices for number of -NH group connected with two single bonds. Its positive contribution in the QSAR model implies that secondary or primary amides will lead to increases potency for the Ang II activity. The next most important descriptor influencing activity variation is T_2_F_1 and is directly proportional to the activity. This descriptor indicates that increase in the count of number of double bounded atoms (i.e. any double bonded atom, T_2) separated from fluorine atom by 1 bond in a molecule will lead to positive effect on the activity. The model is validated by α_ran_r2 = 0.0000, α_ran_q2 = 0.00032, α_ran_pred_r2 = 0.0000, best_ran_r2 = 0.00537, best_ran_q2 = 2.6538, Z score_ran_r2 = 5.47621 and Z score_ran_q2 =1.5874.The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance. The observed and predicted pIC50 along with residual values and Correlation matrix are shown in Table 3 and Table 5. The plot of observed vs. predicted activity is shown in Figure 2.

Table 5: Correlation matrix for QSAR model- 2

	pIC50	SsBrE-Index	SssNHE-index	T_2_F_1	SaaCHcount
pIC50	1.0000				
SsBrE-Index	0.5842	1.0000			
SssNHE-index	0.1642	0.4875	1.0000		
T_2_F_1	0.3659	0.6532	0.7685	1.0000	
SaaCHcount	0.2653	0.4087	0.6732	0.8743	1.0000

Table 6: Correlation matrix for QSAR model 3

	pIC50	SssssCE-index	vdWSurfaceArea	SssNHE-index
pIC50	1.0000			
SssssCE-index	0.3798	1.0000		
vdWSurfaceArea	0.4873	0.7984	1.0000	
SssNHE-index	0.2871	0.3487	0.7632	1.0000

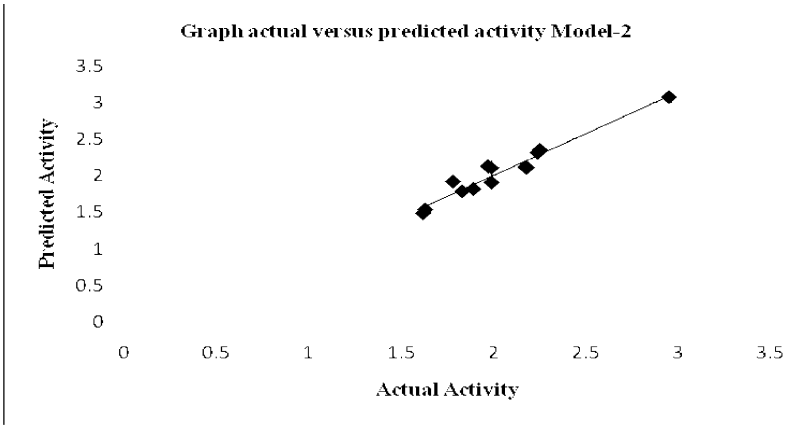


Fig. 2: Plot of actual versus predicted activity for model 2

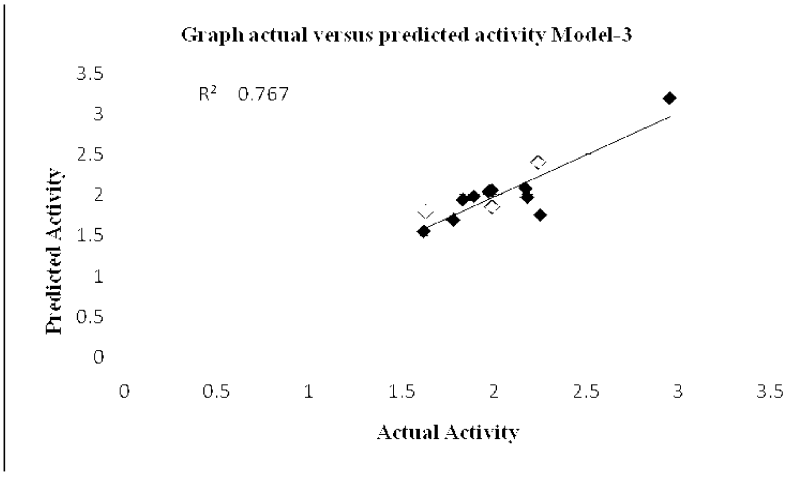


Fig. 3: Plot of actual versus predicted activity for model 3

pIC_{50} = + 2.4370 (SssssCE-index) + 0.2706 (vdWSurfaceArea) + 1.1677 (SssNHE-index) + 2.5783
Optimum components = 3, degree of freedom = 21, n = 13, r^2 = 0.7863, q2 = 0.7164, F test =36.864, r^2 se = 0.3316, q2 se = 0.6934, pred_r^2 = 0.7095, pred_r2se = 0.3276

The statistically significant model 3 using the analysis method having 0.7863 as the coefficient of determination (r^2) was considered. Model 3 can explain 78.63 % of the variance in the observed activity values. It shows an internal predictive power (q^2 = 0.7164) of 71%

and a predictivity for the external test set (pred_r^2 = 0.7095) of about 70% and degree of freedom 21. The model is validated by α_ran_r2 = 0.00064, α_ran_q2 = 0.001, α_ran_pred_r2 = 0.0001, best_ran_r2 = 0.3701, best_ran_q2 = 0.8854, Z score_ran_r2 = 4.5730 and Z score_ran_q2 = 2.5782.The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance. The observed and predicted pIC50 along with residual values and Correlation matrix are shown in Table 3 and Table 6. The plot of observed vs. predicted activity is shown in Figure 3. In this QSAR equation, the positive contribution of SssssCE-index on the biological activity indicated that the increase in dipole moment of molecule leads to better Ang II activity.SssssCE-index is Electro topological state indices for number of carbon atom connected with four single bonds. Its positive value suggests that increasing the number of such carbons will lead to better Ang II potency. This type of electro topological property provides flexibility hence better fitting into the receptor cavity. The positive coefficient of vdWSurfaceArea showed that increase in vdWSurfaceArea is beneficial for the activity. SssNHE-index describes Electro topological state indices for number of -NH group connected with two single bonds. Its positive contribution in the QSAR model implies that secondary or primary amides will lead to increases potency for the Ang II activity.

CONCLUSION

The above study leads to the development of statistically significant QSAR model, which allows understanding of the molecular properties/features that play an important role in governing the variation in the activities. In addition, this QSAR study allowed investigating influence of very simple and easy-to-compute descriptors in determining biological activities, which could shed light on the key factors that may aid in design of novel potent molecules.The good correlation between experimental and predicted biological activity for Thirteen compounds in the test set further supports the reliability of the constructed QSAR model.Multiple Linear Regression method is giving very significant results. The descriptor SaaNE Index, SssssCE-index and SsBrE-Index were common in all three models suggest importance of Electrotopological, Cluster and alignment independent descriptors.

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