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Exploration of Quantitative Structure Activity Relationship Studies on a Series of Substituted Quinazolinones as Angiotensin II AT_1 Receptor Antagonists

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Abstract: A series of 2, 3, 6 substituted-4(3H) Quinazolinones were subjected to QSAR analysis. The QSAR study was carried out on V-life Molecular Design Suite software and the derived best QSAR model was derived by partial least square (forward) regression method. The whole dataset was divided into training set (13 compounds) and test set (3) compounds). The statistically significant model with high correlation coefficient (r2) 0.8215 was selected for further study. The model was further validated by means of crossed squared correlation coefficient (q2) 0.8346 and pred_r2 (0.8173) which shows model has good predictive ability. Higher value of F statics 57.543 also validates significance of model, Degree of freedom11.The physicochemical descriptor SssCH2count and alignment-independent descriptors T_N_O_6, T_C_C_2, SsCH3count and Rotatable Bond Count were found to show significant correlation with biologic activity in Quinazolinones. The generated QSAR model revealed the importance of structural, thermodynamic and electrotopological parameters. The quantitative structure activity relationship provides important structural insight in designing of potent Antihypertensive compounds.

Key words: Ang II · QSAR · Quinazolinones · AT_1 · Antihypertensive

INTRODUCTION

The renin-angiotensin system (RAS) plays a key role in regulating cardiovascular homeostasis and electrolyte fluid balance in normotensive and hypertensive subjects [1]. The RAS is a key element in blood pressure regulation and electrolyte/fluid homeostasis [2]. Renin, a proteolytic enzyme produced mainly in the juxtaglomerular apparatus of the kidney, acts on the circulating alpha globulin angiotensinogen produced by the liver to form the decapeptide Asp-Arg-Val-Tyr-Ileu-His-Pro-Phe-His-Leu, named angiotensin I. Angiotensin I is relatively inert but is converted to the active octapeptide Asp-Arg-Val-Tyr-Ileu-His-Pro-Phe, named as angiotensin II by angiotensin-converting enzyme (ACE) present in lungs and other organs. Activation of the renin-angiotensin cascade begins with renin secretion from the juxtaglomerular apparatus of the kidney and culminates in the formation of the octapeptide angiotensin II (Ang II), which then interacts with specific receptors present in different tissues [3]. Two basic types of receptors, both having a broad distribution, have been characterized so far: the AT_1 receptor, responsible for the majority of effects attributed to this peptide and the AT_2 receptor, with a functional role yet uncertain[4]. The main effects of Ang II are the regulation of blood pressure through vasoconstriction, thereby affecting an increase in vascular resistance, the regulation of volemia through the stimulated release of vasopressin and aldosterone, which induces saline retention and the regulation of the adrenocorticotropic hormone (ACTH). Thus, reducing the levels of Ang II by inhibition of one of the RAS enzymes or directly blocking the Ang II receptors is in theory a good approach for treating hypertension, confirmed by the success of angiotensin-converting enzyme (ACE) inhibitors as antihypertensive [5].Substantial effort has been made to find renin inhibitors, although orally active agents have only recently been reported [6]. Starting from the initial leads researchers [7] at DuPont [8] discovered losartan, the first orally active AT_1 selective nonpeptide. 2D-QSAR does not involves complex alignment or assumptions on conformations and therefore they can easily be applied to large compound sets, both in model building and in model application to new compounds. In such methods one has the choice among a wide variety of molecular descriptors independent on 3D conformation, for example, topological descriptors, simple molecular properties such as the molecular weight and easily

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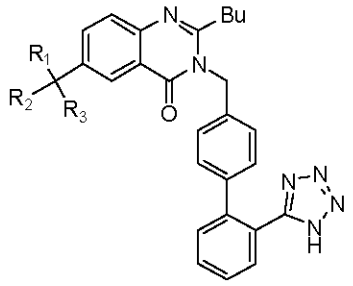
calculated physicochemical properties such as ClogP or atomic partial charges [9]. Numerous data sets reported in the literature were subjected to QSAR analysis for the purpose of designing novel angiotensin II receptor antagonists [10-15]. In the present study, we have performed the quantitative structure activity relationship analysis by PLS Regression methods are used to build a QSAR model in the form of a mathematical equation. This equation explains variation of one or more dependent variables (usually activity) in terms of independent variables. Here we propose a general model for the antagonist and present minimal structural requirement for an Angiotensin II antagonist. These results should serve as a guideline in designing more potent and selective Ang II antagonist.

MATERIALS AND METHODS

The Ang II receptor antagonistic activity data of substituted-4(3H) Quinazolinones derivatives were taken from the reported work [16]. The biological activities of these sixsitten compounds were expressed in terms of IC_{50} values for angiotensin II receptor antagonists. 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). All the computational studies were performed on Compaq (Pentium-D) computer using the software VLife MDS 3.5[17].

Data Set Preparation: The molecular structure of all the sixteen molecules were sketched using VLife MDS 3.5 software in the 2D builder module and then the structures were converted to 3D space for further analysis.Molecules were sketched using the same. Optimizations of the sketched compounds were done by batch minimization process using force field computations of the VLife MDS. Each compound was subjected to energy minimization and batch optimization using Merck Molecular Force Field (MMFF), fixing Root Mean Square Gradients (RMS) to 0.01 kcal/mol A° and the iteration limit to 10,000[18]. The optimized batch of molecules was selected for calculation of the physiochemical descriptors. The descriptor pool was shrieked by eliminating out the descriptors with constant and near-constant values. Further diminution in the descriptor pool was done by ousting the descriptors that are highly degenerate and

Table 1: Biological activity data and chemical structure



Comp.	R1	R2	R3	IC50(nM)	pIC50
1	H	H	OH	10	1.00
2	H	Me	OH	9	0.95
3	H	Et	OH	12	1.08
4	Me	Me	OH	9	0.95
5	H	H	NH_2	15	1.17
6*	H	Me	NH_2	14	1.14
7	H	t-Bu	OH	>1000	3.00
8	H	CH_2OH	OH	>1000	3.00
9*	H	H	OMe	18	1.25
10	H	Me	OMe	7	0.84
11	H	Et	OMe	5	0.69
12	Me	Me	OMe	6	0.78
13*	H	Ph	OMe	9	0.95
14	H	Me	NHAc	6	0.78
15	H	H	OPh	130	2.11
16	H	H	O-2-Py	130	2.11

Table 2: Description of descriptor used in the QSAR study

Sss CH2 count	Rotatable Bond Count	4Path Count	Chi3 cluster	Sss NHE-index	T_N_O_6,	T_C_C_2	Hydrogen Count
47.584	21.087	14.57972	12.92017	10.9032	2	3	4
56.071	25.07034	17.54605	15.59722	13.39497	6	4	2
43.851	45.40362	20.33829	12.82991	11.37088	6	4	2
45.403	23.20853	16.10089	13.9198	11.64561	2	3	4
51.891	23.20853	16.11772	13.8452	11.63439	0	0	0
10.834	19.96486	12.12931	19.96486	13.18868	0	0	0
62.543	27.45117	19.10089	16.04112	13.13874	2	3	4
64.378	28.15828	19.60089	16.39467	13.39561	0	0	0
62.543	27.45117	19.11772	15.96652	13.13439	0	0	0
56.759	24.62275	17.10089	14.6269	12.14561	2	3	4
55.985	24.2001	17.13536	15.06971	12.92814	2	3	4
55.561	6.394712	4.910768	3.590345	6.394712	2	3	4
57.038	25.32985	17.60089	14.98046	12.39561	2	3	4
64.378	28.15828	19.60089	16.39467	13.39561	2	3	4
59.972	26.41564	17.80799	16.18756	13.10272	2	3	4
58.424	25.99299	17.86934	16.51248	13.77069	2	3	4

Table 3: Unicolumn statistics of the training and test sets

Data Set	Average	Max	Min	StdDev	Sum
Training	12.653	8.0742	6.7643	0.8753	54.7643
Test	6.6743	5.8553	4.6532	0.5945	18.9854

difficult to interpret. The remaining topological and electro-topological descriptors were taken into account for the reported correlation analysis and also the descriptors those were showing very low correlation with inhibitory activity removed. The energy-minimized geometry was used for the calculation of the various 2D descriptors (Individual, Chi, ChiV, Path count, ChiChain, ChiVChain, Chain path count, 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. Descriptors included in a reasonable QSAR equation should exhibit low inter correlation and thus behave as independent variables. Inter-correlation between the descriptors was used to select descriptors for the equation and the quality of fit for a regression equation was assessed as relative to its correlation coefficient and standard deviation. The F value represents the level of statistical significance of the regression. Quality of the selected models was further ascertained from cross-validated squared correlation coefficient (q^2). The descriptors selected for modeling activity of the 2, 3, 6 substituted-4(3H) Quinazolinones derivatives are summarized in (Table 2). Partial least square regression (PLSR) method of model building has been intensively used in QSAR analysis and this approach leads correct and highly predictive models. The sphere exclusion (SE) method [19] was adopted for division of training and test data set comprising of thirteen and three molecules, respectively, with dissimilarity value of 5.1 where the dissimilarity value gives the sphere exclusion radius. In classical sphere-exclusion algorithm the molecules are selected whose similarities with each of the other selected molecules are not higher than a defined threshold. Each selected molecule generates a hyper-sphere around itself, so that any molecule inside the sphere is excluded from the selection in the train set and driven toward the test set. The number of compounds selected and the diversity among them can be determined by adjusting the radius of the sphere (R). This algorithm allows construction of the data sets by using descriptor space occupied by the representative points, such that the test set molecules represent a range of biological activities similar to the training set; thus, the test set is truly a representative of the training set. The unicolumn statistics of test and training sets (Table 3) further reflected the correct selection of test and training sets, as the maximum of the training set was more than that of the test set and the minimum of the training set was less than or equal to that of the test set. This showed that the test set was interpolative, i.e., derived within the minimum–maximum range of the training set. The average and standard deviation of the training and test set provided insight into the relative difference in mean and point density distribution (along the mean) of the two sets.

Statistical Analysis: Models 1, 2, 3 and 4 were generated by using three significant statistical methods, namely, partial least square analysis. The cross-validation analysis was performed using the leave-one-out method. In the selected equations, the cross-correlation limit was set at 0.5, the number of variables at 10 and the term selection criteria at r^2. An F value was specified to evaluate the

significance of a variable. The higher the F value, the more stringent was the significance level: F test ''in'' as 4 and F test ''out'' as 3.99. The variance cut-off was set at 0 and scaling was auto scaling in which the number of random iterations was set at 100.This is done to test the internal stability and predictive ability of the QSAR models. Developed QSAR models were validated by the following procedure; 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 [20].The cross-validated coefficient, q^2, is calculated using the following equation:

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

where *yi* and *yi* are the actual and predicted activity of the *i*th molecule in the training set, respectively and *ymean* 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 pIC50 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.

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

Where *yi* and *yi* are the actual and predicted activity of the *i*th molecule in the test set, respectively and *ymean* 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[21]. A Z score value is calculated by the following formula:

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

Where *h* is the q2 value calculated for the actual dataset, ì the average q2 and ó is its standard deviation calculated for various iterations using models build by different random datasets. If Z score value is less than 4.0; otherwise it is calculated by the formula as given in the literature. For example, a Z score value greater than 3.10 indicates that there is a probability (á) of less than 0.001 that the QSAR model constructed for the real dataset is random. The randomization test suggests that all the developed models have a probability of less than 1% that the model is generated by chance.

Feature Selection and Model Development: An integral aspect of any model-building exercise is the selection of an appropriate set of features with low complexity and good predictive accuracy. This process forms the basis of a technique known as feature selection [22] or variable selection. In stepwise (SW) forward variable selection algorithm, the search procedure begins with developing a trial model step by step with a single independent variable and to each step; independent variables are added one at a time, examining the fit of the model by using the PLS cross-validation procedure. Thus, the model is repeatedly altered from the previous one by adding or removing a predictor variable in accordance with the 'stepping criteria'. The method continues until there is no more significant variable remaining outside the model.

Partial Least Squares Regression Method: PLS is a generalization of regression, which can handle data with strongly correlated and/or noisy or numerous X variables [23]. It gives a reduced solution, which is statistically more robust than MLR. The linear PLS model finds "new variables" (latent variables or X scores) which are linear combinations of the original variables. Cross-validation is a practical and reliable method for testing this significance. PLS is normally used in combination with cross-validation to obtain the optimum number of components. This ensures that the QSAR models are selected based on their ability to predict the data rather than to fit the data [24].

RESULTS AND DISCUSSION

In the 2D QSAR several models were generated for the given or selected members of training and test sets and the corresponding best models are reported herein. This method utilizes the active analogue principle that lies at the foundation of medicinal chemistry [24-28]. Although, generation of QSAR models with good statistical significance is of paramount importance, the models should also exhibit good predictive ability. The predictive ability of the models was gauged by a cross validation procedure following a leave-one-out scheme. All the models exhibit high q^2 and low r^2_se and q^2se values confirm their excellent predictive potential. The magnitude of a descriptor could be used as a guideline to improve the antihypertensive activity of molecules.

Table 4: Comparative observed and predicted activities (LOO) of QSAR models

Comp.	Observed activity	Predict activity-1	Predict activity-2	Predict activity-3	Predict activity-4
1	1.00	0.76	0.59	0.85	0.89
2	0.95	1.03	1.27	0.64	0.79
3	1.08	0.86	0.57	1.28	1.13
4	0.95	0.71	1.01	0.63	0.75
5	1.17	0.99	0.89	0.89	1.09
6	1.14	0.98	1.17	1.08	1.18
7	3.00	2.82	2.94	3.22	3.08
8	3.00	2.88	2.78	2.95	2.86
9	1.25	1.14	1.01	1.06	1.16
10	0.84	0.63	0.72	0.93	1.08
11	0.69	0.58	0.64	0.56	0.73
12	0.78	0.84	0.64	0.69	0.83
13	0.95	1.08	0.82	1.02	1.11
14	0.78	0.6	0.91	0.55	0.95
15	2.11	1.84	2.06	1.78	2.03
16	2.11	1.91	1.98	1.83	2.18

Table 5: Correlation matrix indicating inter-correlation between descriptors for best model 1

	pIC50	SssCH2 count	SsCH3 count	T_N_O_6	T_C_C_2	Rotatable Bond Count
pIC50	1					
SssCH2count	0.6953	1				
SsCH3count	0.3254	0.6573	0.7452	1		
T_N_O_6	0.3659	0.6532	0.7685	0.8731		
T_C_C_2	-0.065	-0.1426	-0.3616	-0.5743	1	
Rotatable Bond Count	0.1247	0.3275	0.5422	0.6587	0.7655	1

Model-1

pIC50= +2.8576(SssCH2count)-1.0656(SsCH3count) +0.4387(T_N_O_6)+0.6832(T_C_C_2)+0.95493(Rotatable Bond Count) +1.6984

n = 16, Degree of freedom = 11, r2 = 0.8764, q^2 = 0.8346, F test = 57.543, r^2se = 0.2386, q^2_se = 0.3861, pred_r^2 = 0.8173, pred_r^2se = 1.3417.

The derived model shows good correlation between biological activity and parameters SssCH2count, T_N_O_6, T_C_C_2, SsCH3count and Rotatable Bond Count as the correlation coefficient r = 0.8365.The model-1 fulfills the selection criteria's like correlation coefficient r^2 >0.8(0. 8764) for activity with low standard error of squared correlation coefficient r^2_se <0.3(0.2386) show the relative good fitness of the model and F value >11 times than tabulated F value show the 99% statistical significance of the regression model. The validation criteria for selection of the model are cross validated squared correlation coefficient q^2 >0.8(0.8346) for training set and pred_r^2>0.40 (0.8173) for test set. However, a high q^2 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 the present study. The observed and predicted pIC_{50} along with residual values and Correlation matrix are shown in (Table 4) and (Table 5). The model incorporates four parameters $SssCH_2$count, T_N_O_6, T_C_C_2, $SsCH_3$count and Rotatable Bond Count and their corresponding values for each molecule in the selected model. The descriptor $SssCH_2$count in the model represents the electro-topological state indices for number of $–CH_2$ group connected with two aromatic double bonds. As a positive contributing descriptor, T_N_O_6 is an alignment-independent descriptor influencing activity variation and is directly proportional to activity. The descriptor T_N_O_6 is the number of atoms separated from the nitrogen atom by six bonds, indicating that the presence of substituents with nitrogen atoms (e.g., $–NO_2$, $–N(CH3)_2$, $–NHCOCH_3$, $NHCOCH_2CH_3$) at the phenyl ring in the ortho position will lead to a positive effect on the activity. The descriptor T_C_C_2 (i.e., the number of double-bonded atoms separated from the carbon atom by two bonds) indicates a positive

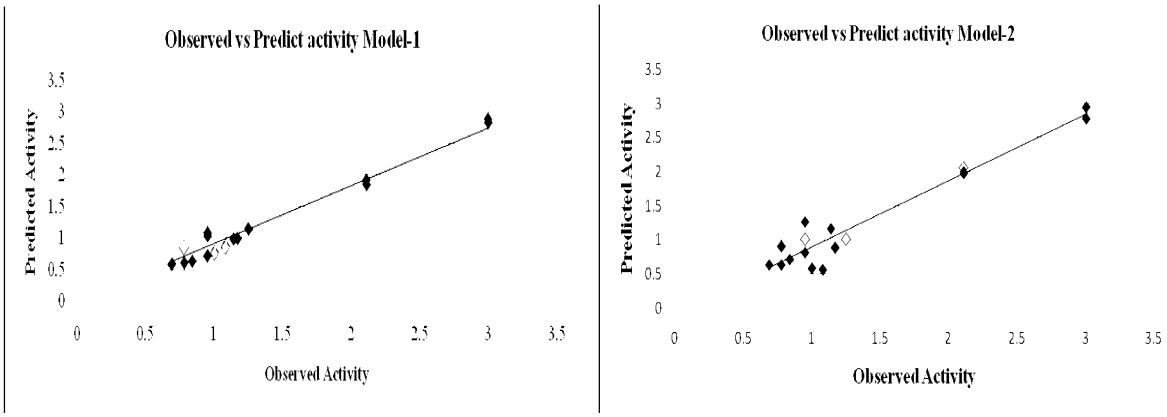


Fig. 1: The plot of observed versus predicted activity for model 1 and 2

contribution to the biologic activity. It suggests that the mono substituent with a carbon atom in the position of the phenyl ring is detrimental to activity. Rotatable Bond Count refers to number of rotatable bonds in the molecules. The slightly positive term associated with the descriptor in QSAR model indicates that fractional increase in the rotatable bonds in the molecule is beneficial for Ang II activity. The model is validated by á_ran_r^2 = 0.00004, á_ran_q^2 = 0.001, á_ran_pred_r^2 = 0.00021, best_ran_r^2 = 0.4316, best_ran_q^2 = 0.1649, Z score_ran_r^2 = 6.3654 and Z score_ran_q^2 = 8.4175.The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance.

Model-2

pIC50 = + 0.8514 (PolarSurfaceAreaIncluding P and S) + 1.0965 (Hydrogen Count) + 2.0743 (SssNHE-index) +5.2743

Optimum components = 3, degree of freedom = 11, n = 16, r^2 = 0.8393, q^2 = 0.7842, F test =42.638, r^2 se = 0.6733, q^2 se = 0.2754, pred_r^2 = 0.7405, pred_r^2se = 0.2754

The statistically significant model 2 using the analysis method having 0.8393 as the coefficient of determination (r2) was considered. Model 2 can explain 83.93% of the variance in the observed activity values. It shows an internal predictive power (q^2 = 0.7842) of 78% and a predictivity for the external test set (pred_r^2 = 0.7405) of about 74% and degree of freedom 11. The model is validated by á_ran_r2 = 0.00001, á_ran_q2 = 0.001, á_ran_pred_r2 = 0.0001, best_ran_r^2 = 0.1074, best_ran_q^2 = 0.2751, Z score_ran_r^2 = 2.4876 and Z score_ran_q^2 = 6.1645.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 pIC_{50} along with residual values are shown in (Table-5). 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. SssNHE-index is describes Electro topological state indices for number of –NH group connected with two single bonds. Its positive contribution in the QSAR model implies that will lead to increases potency for the instead of COOH group. 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. PolarSurfaceAreaIncluding P and S descriptor polar surface area excluding P and S (i.e., phosphorus and sulfur) plays a most important role in determining activity. This descriptor signifies the total polar surface area excluding phosphorus and sulphur. The Hydrogen Count descriptor is a type of element count descriptor showing the number of hydrogen atoms in a compound, suggesting double, triple, or aromatic substituents over alkyl substituents.It is apparent from the equation that the H donors count, a topologic descriptor subclassed as an individual descriptor suggesting the number of hydrogen bond donor atoms plays a pivotal role in determining activity.

Model-3

pIC50 = + 2.5477 (4PathCount) + 0.2598 (Chi3cluster) - 1.426 (SssNHE-index) +0.6532

Optimum components = 3, degree of freedom = 11, n = 16, r^2 = 0.8062, q^2 = 0.7438, F test =38.583, r^2 se = 0.2641, q^2 se = 0.5732, pred_r^2 = 0.6831, pred_r^2se = 0.4869

The derived model shows good correlation between biological activity and parameters 4PathCount, Chi3cluster and SssNHE-index as the correlation coefficient r = 0.8549 and the model explains about 85% variance in Ang II activity exhibited by Quinazolinones derivatives. The low standard error of r2_se= 0.2641 demonstrates accuracy of the model. The model show overall significance level better than 99.99%, with F= 38.583 against values of 99.99% significance. The leave-one-out procedure was used for internal validation of the model. In this procedure high cross validated r2 (q^2= 0.7438) and low q^2_se=0.5732 value, reflects the very good internal predictive power of the model. The observed and predicted pIC50 along with residual values are shown in (Table 4).The descriptor SaaNE-index in the model represents the electro-topological state indices for number of nitrogen atoms connected with two aromatic double bonds. It shows presence of lone pair of electrons on nitrogen atom which is representing the interaction between drug and receptors. The negative correlation of the descriptor in the model indicates that electro-topological properties of the nitrogen atoms present in aromatic rings. The 4Pathcount is topological parameter which can signify the total number of fragments of fourth order (four bond path) in compound. It is positively correlated with inhibitory activity so, it may be inferred that increasing the branching of compound is favorable for activity and Chi3cluster positive indicated increases activity.

Model 4

pIC50 = - 0.2456 (YcompDipole) - 0.5020 (SaasCE-index) + 0.1226 (StNE-index) + 0.3207 (T_N_O_7) + 6.3135

Optimum components = 3, degree of freedom = 11, n = 16, r^2 = 0.8432, q^2 = 0.7854, F test = 36.321, r^2_se = 0.4312, q^2_se = 0.6588, pred_r^2 = 0.7418, pred_r^2se = 0.08743, ZScore $Q^{\wedge 2}$ = 6.7643, Best Rand $Q^{\wedge 2}$ = 0.3217.

Model shows 84.32 % variance in the observed activity values. The low standard error of r^2_se = 0.4312 demonstrates accuracy of the model. The F test value, 36.321 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, 0.7854, indicates good internal prediction power of the model. Another parameter for predictivity of test set compounds is high pred_r^2 = 0.7418, which shows good external predictive power of the model. The negative coefficient of YcompDipole shows that increase in YcompDipole is detrimental for the activity. As a positive contributing descriptor, T_N_O_7 is an alignment independent descriptor influencing activity variation and is directly proportional to activity.

The descriptor SaaCE-index in the model represents the electro-topological state indices for number of carbon atoms connected with two aromatic double bonds. It shows presence of lone pair of electrons on nitrogen atom which is representing the interaction between drug and receptors. The descriptor StNE-index plays a pivotal role in determining activity. This suggests that the presence of quinazolinones derivatives group at R1 position would increase the activity.

CONCLUSION

The 2D QSAR studies were conducted with a series of angiotensin II antagonists and some useful molecular models were obtained. The physicochemical and alignment-independent descriptors were found to have an important role in governing the change in activity. The descriptors showed by QSAR study can be used further for study and designing of new compounds. Consequently this study may prove to be helpful in development and optimization of existing antihypertensive agents of this class of compounds. Hence, these models are very useful for further optimization of antihypertensive activities. The current study provides better insight into the designing of more potent antihypertensive agents in the future before their synthesis.

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