ORIGINAL RESEARCH ARTICLES

2D QSAR STUDIES OF NOVEL TRIAZOLINONE DERIVATIVES AS ANGIOTENSIN II ANTAGONISTS USING TOPOLOGICAL DESCRIPTORS

Mukesh C. Sharma[a]* and D. V. Kohli[b]

(Received 20 January 2021) (Accepted 13 January 2022)

ABSTRACT

Quantitative Structure Activity Relationship (QSAR) model on a series of triazolinone derivatives acting as angiotensin II receptor using partial least squares regression analysis was performed to compute the relationship with 2D structure descriptors. The computational studies were performed with trial version V-life Molecular Design Suite software. The developed models were validated using an internal predictive power and predictivity for the external test set of 0.8653, and 0.7981 were obtained. The F test value shows the overall statistical significance level. Models developed in this study have potential application in the prediction of binding affinity for the newly synthesized compounds.

Keywords: QSAR, Triazolinone, Angiotensin II receptor, partial least squares, Topological, electrotopological, hydrophobicity

INTRODUCTION

The renin-angiotensin-aldosterone system (RAAS) is intricately involved in the pathophysiology of several diseases, including hypertension, congestive heart failure and chronic kidney disease of all types including diabetic nephropathy. Pharmaceutical RAAS blockade has is a common and successful strategy in each of these conditions[1-4]. Angiotensin II receptor antagonists, angiotensin converting enzyme (ACE) inhibitors and renin inhibitors have all been used to investigate the involvement of the renin–angiotensin system in essential hypertension[5]. 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[6]. RAAS system blockade can take place at several levels. RAAS-blockers include direct renin inhibitors (DRIs) which block production of renin, ACEIs block conversion of AT_1 to AT_2 by blocking angiotensin-converting enzyme, ARBs antagonize the effect of aII on AT_1 receptors and aldosterone antagonists which block the effect of aldosterone[7]. AT_1 receptor blockers (ARBs) are selective non-peptide antagonists in clinical use for the treatment of high blood pressure and are also being examined for various other human cardiovascular disorders[8]. Eight ARBs – azilsartan, eprosartan, candesartan, irbesartan, losartan, telmisartan, olmesartan and valsartan – are available for clinical use.

QSAR studies have been widely used to understand the relationship between the structure of the molecule and biological activity. Quantitative structure–activity relationship (QSAR) study finds correlations between biological activities and molecular descriptors of different classes of compounds[9]. However, some limitations spurred the appearance of three-dimensional quantitative structure-activity relationship (3D-QSAR). QSAR and molecular docking technology have been extensively employed in drug virtual screening and potential molecular targets prediction, which may shorten the cycle of the drug development[10]. Earlier studies in our laboratory in developing a model to predict the biological activity of compounds 2,4,5-trisubstituted triazolinones aryl and nonaryl derivatives as angiotensin II AT1 receptor antagonists[11]. Studying the two-dimensional quantitative structure activity relationships for the synthesized analogs explored the observed pharmacological properties as well as validated the observed activity of the new chemical entities. The objective of this study was to develop best QSAR model to find features which are responsible for biological activity of angiotensin II AT_1 receptor antagonists[12].

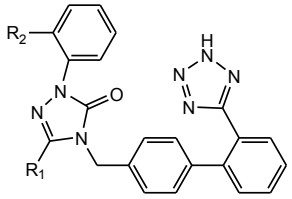
[a] Department of Pharmaceutical Chemistry, School of Pharmacy, Devi Ahilya University, Khandwa Road, Indore - 452 001, Madhya Pradesh, India

[b] Department of Pharmaceutical Sciences, Dr H. S. Gour Vishwavidyalaya, Sagar - 470 003, Madhya Pradesh, India

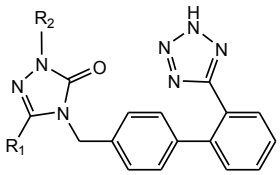
*For Correspondence: E-mail: drmukeshcsharma@gmail.com

https://doi.org/10.53879/id.59.05.12852

Table I : Structures of 2,4,5-trisubstituted triazolinones with their activities



Compound 1-33



Compound 34-55

S. No.	R_1	R_2	IC_{50} [a]	pIC_{50} [b]
1	n-Bu	H	22	1.342
2	n-Bu	2-CH_3	4.1	0.612
3[c]	n-Bu	2-Cl	2.4	0.38
4	n-Bu	2-NO_2	0.85	-0.07
5[c]	n-Bu	2-OCH_3	6.6	0.819
6	n-Bu	3-CH_3	18	1.255
7	n-Bu	3-Cl	120	2.079
8[c]	n-Bu	3-NO_2	43	1.633
9	n-Bu	3-OCH_3	15	1.176
10	n-Bu	4-CH_3	16	1.204
11[c]	n-Bu	4-Cl	69	1.838
12	n-Bu	4-NO_2	80	1.903
13	n-Bu	4-OCH_3	5	0.698
14[c]	n-Bu	4-C_2H_5	27	1.431
15	n-Bu	4-F	21	1.322
16	n-Bu	4-$COOCH_3$	33	1.518
17	n-Bu	2-i-C_3H_7	1.4	0.146
18	n-Bu	2-Phenyl	3.6	0.556
19[c]	n-Bu	2-CH_2Phenyl	11	1.041
20	n-Bu	2-F	7.7	0.886
21[c]	n-Bu	2-Br	2	0.301
22	n-Bu	2-CF_3	1.2	0.079
23	n-Bu	2-$COOCH_3$	5.6	0.748
24	n-Bu	2-COOH	115	2.06
25	n-Bu	2-NH_2	100	2.00
26	n-Bu	2-$N(CH_3)_2$	3.2	0.505
27[c]	n-Bu	2,6-Cl_2	5.8	0.763
28	n-Bu	2-NO_2,4-OCH_3	0.74	-0.130
29	n-Bu	2,3,4,5,6-F_5	17	1.230
30[c]	n-Pr	2-Cl	14	1.146
31	n-Pentyl	2-Cl	5.7	0.755
32	n-Pr	2-NO_2	9.5	0.977
33[c]	n-Pentyl	2-NO_2	0.93	-0.0315
34	n-Bu	2-pyridyl	79	1.897
35	n-Bu	H	60	1.778
36	n-Bu	CH_3	70	1.845
37	n-Bu	C_2H_5	10	1.000
38	n-Bu	C_3H_7	8.2	0.913
39[c]	n-Bu	C_4H_9	2.9	0.462
40	n-Bu	*i*-propyl	7.7	0.886
41	n-Bu	*i*-butyl	3.2	0.505
42	n-Bu	*s*-butyl	1.8	0.255
43[c]	n-Bu	CH_2COOCH_3	17	1.23
44	n-Bu	Benzyl	4.6	0.662
45[c]	n-Bu	CH_2(c-Hexane)	2.9	0.462
46	n-Bu	(2-CH_3)benzyl	11	1.401
47	n-Bu	(3-CH_3) benzyl	12	1.079
48	n-Bu	(α-CH_3) benzyl	4.9	0.69
49[c]	n-Bu	(2-$COOCH_3$) benzyl	11	1.041
50	n-Bu	(3-$COOCH_3$) benzyl	110	2.041
51	n-Bu	(4-$COOCH_3$) benzyl	23	1.361
52[c]	n-Bu	(α -$COOCH_3$) benzyl	12	1.079
53	n-Bu	(2-COOH) benzyl	490	2.690
54	n-Bu	(α -COOH) benzyl	68	1.832
55	n-Bu	$CH_2C_6F_6$	32	1.505

[a] *IC_{50} or inhibition*

[b] *-log IC_{50} to generate equation*

[c] *Indicates the compounds considered in the test set in 2D QSAR*

MATERIALS AND METHODS

Dataset collection and geometry optimization

2D QSAR were performed using the V-Life Molecular Design Suite 3.5[13]. The data set used for the QSAR analyses contains fifty-five compounds belonging to 2,4,5-trisubstituted triazolinones derivatives as AT_1 receptor antagonists[12]. The biological activity values

[IC_{50} (nM)] reported in the literature were converted to their molar units and then further to negative logarithmic scale (pIC_{50}) and subsequently used as the dependent variable for the QSAR analysis. The values of IC_{50} along with the structure of the fifty-five compounds in the series is presented in Table I. The energy minimization was carried out using Merck Molecular Force Field (MMFF), by fixing the maximum number of cycles at 10,000 and root mean square gradient value 0.001 kcal mol^{-1} using analytical gradient type and distance-dependent function having constant value of 1.0[14].

Division of dataset

The dataset of the studied molecules was partitioned into a training set used to develop the QSAR model and a test set employed for the external validation of the developed model. The sphere exclusion method[15] was adopted for division of training and test data set comprising of forty and fifteen molecules, respectively, with a dissimilarity value of 4.9, where the dissimilarity value gives the sphere exclusion radius using pIC_{50} activity field as dependent variable and various 2D descriptors as independent variables. Unicolumn statistics for training set and test set were generated to check correctness of selection criteria for training and test set compounds (Table II)[13].

Table II: Unicolumn statistics of training and test sets for activity

Data Set	Average	Max	Min	SD	Sum
Training	-1.3218	0.3692	-2.2846	0.8198	-24.6328
Test	-0.4854	0.8596	-2.2489	0.4852	-9.4735

Max-maximum, Min-minimum, SD-standard deviation

A total of 318 descriptors were calculated by using VLife Sciences Molecular Design Suite, which was subsequently reduced to 248 descriptors. The descriptors having the same value or almost same value or highly correlated with other descriptors were removed initially. The physico-chemical descriptors calculated are; Individual Descriptors, Retention Index, Atomic valence connectivity index, Path count, Chi chain, ChiV chain, Cluster, Path cluster, Kappa, Element count, Estate numbers, Estate contributions, Information theory index and Polar surface area. In this study, to calculate AI descriptors, we have used following attributes, 2 (double bonded atom), 3 (triple bonded atom), C, N, O, S, H, F, Cl, Br and I and the distance range of 0–7. Various alignment- independent (AI) descriptors were also calculated[16].

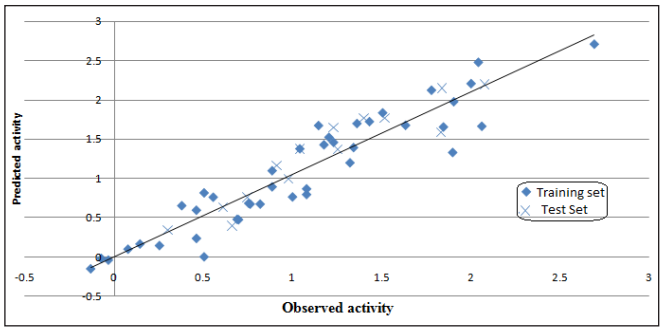


Fig. 1(a): Graph of observed and predicted activities of the training and test set compounds by model 1

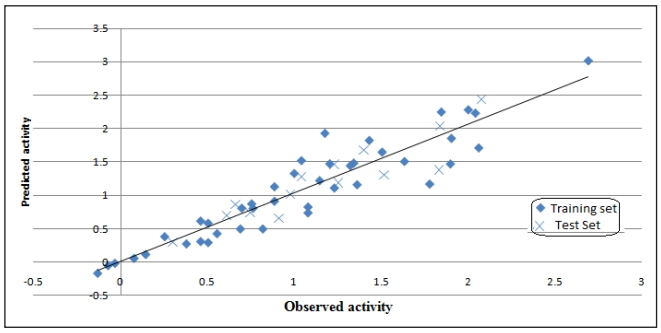


Fig. 1(b): Graph of observed and predicted activities of the training and test set compounds by model 2

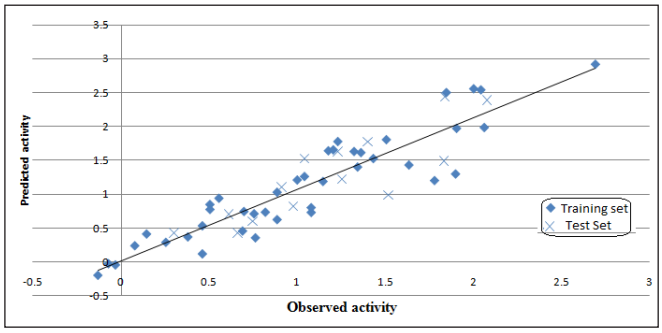


Fig. 1(c): Graph of observed and predicted activities of the training and test set compounds by model 3

Model building

Statistical parameters of the model were reviewed and evaluated to ascertain its fitting ability, reliability, predictive ability, stability and robustness of the model generated[17]. The quality assurance of a developed model is guaranteed if the results agreed with global QSAR standard, i.e., $R^2 > 0.6$, $R^2_{pred} > 0.5$, $Q^2 > 0.6$, $P(95\%) < 0.05$, high value of F-test, low values of R^2_{random} and Q^2_{random}[18].

The internal predictability of the models was evaluated in terms of cross validated q^2 [19] by the following equation

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

Table III: Comparative observed and predicted activities through QSAR models

Com	pIC_{50}	Model- 1		Model- 2		Model- 3	
		Pred.	Res.	Pred.	Res.	Pred.	Res.
1	1.342	1.291	0.051	1.489	-0.147	1.398	-0.056
2	0.612	0.595	0.017	0.699	-0.087	0.701	-0.089
3	0.380	0.421	-0.041	0.279	0.101	0.368	0.012
4	-0.07	-0.011	-0.059	-0.046	-0.024	-0.028	-0.042
5	0.819	0.778	0.041	0.503	0.316	0.732	0.087
6	1.255	1.195	0.06	1.185	0.07	1.221	0.034
7	2.079	2.032	0.047	2.436	-0.357	2.386	-0.307
8	1.633	1.707	-0.074	1.513	0.12	1.428	0.205
9	1.176	1.226	-0.05	1.935	-0.759	1.638	-0.462
10	1.204	1.496	-0.292	1.478	-0.274	1.652	-0.448
11	1.838	2.021	-0.183	2.037	-0.199	2.438	-0.6
12	1.903	1.896	0.007	1.859	0.044	1.968	-0.065
13	0.698	0.502	0.196	0.813	-0.115	0.743	-0.045
14	1.431	1.694	-0.263	1.829	-0.398	1.523	-0.092
15	1.322	1.209	0.113	1.45	-0.128	1.628	-0.306
16	1.518	1.711	-0.193	1.306	0.212	0.982	0.536
17	0.146	0.200	-0.054	0.121	0.025	0.411	-0.265
18	0.556	0.623	-0.067	0.432	0.124	0.938	-0.382
19	1.041	1.307	-0.266	1.275	-0.234	1.523	-0.482
20	0.886	0.891	-0.005	0.918	-0.032	0.623	0.263
21	0.301	0.288	0.013	0.293	0.008	0.428	-0.127
22	0.079	0.111	-0.032	0.062	0.017	0.238	-0.159
23	0.748	0.703	0.045	0.732	0.016	0.599	0.149
24	2.06	1.835	0.225	1.716	0.344	1.981	0.079
25	2.000	2.185	-0.185	2.287	-0.287	2.552	-0.552
26	0.505	0. 523	-0.018	0.588	-0.083	0.846	-0.341
27	0.763	0.690	0.073	0.812	-0.049	0.355	0.408
28	-0.130	-0.176	0.046	-0.162	0.0313	-0.198	0.068
29	1.230	1.215	0.015	1.116	0.114	1.774	-0.544
30	1.146	1.471	-0.325	1.226	-0.08	1.186	-0.04
31	0.755	0.781	-0.026	0.879	-0.124	0.709	0.046
32	0.977	1.084	-0.107	1.016	-0.039	0.816	0.161
33	-0.0310	-0.0374	0.0064	-0.0117	-0.0198	-0.0452	0.0137
34	1.897	1.728	0.169	1.476	0.421	1.296	0.601
35	1.778	1.733	0.045	1.175	0.603	1.199	0.579
36	1.845	1.323	0.522	2.254	-0.409	2.496	-0.651
37	1.000	1.062	-0.062	1.334	-0.334	1.207	-0.207
38	0.913	1.021	-0.108	0.654	0.259	1.104	-0.191
39	0.462	0.284	0.178	0.315	0.147	0.118	0.344
40	0.886	0.818	0.068	1.135	-0.249	1.026	-0.14

41	0.505	0.574	-0.069	0.298	0.207	0.773	-0.268
42	0.255	0.208	0.047	0.387	-0.132	0.288	-0.033
43	1.230	1.596	-0.366	1.463	-0.233	1.628	-0.398
44	0.662	0.388	0.274	0.865	-0.203	0.427	0.235
45	0.462	0.427	0.035	0.621	-0.159	0.532	-0.07
46	1.401	1.652	-0.251	1.675	-0.274	1.774	-0.373
47	1.079	0.903	0.176	0.831	0.248	0.729	0.35
48	0.690	0.507	0.183	0.503	0.187	0.455	0.235
49	1.041	1.188	-0.147	1.526	-0.485	1.259	-0.218
50	2.041	2.128	-0.087	2.237	-0.196	2.536	-0.495
51	1.361	1.591	-0.23	1.165	0.196	1.611	-0.25
52	1.079	0.928	0.151	0.743	0.336	0.8	0.279
53	2.690	2.521	0.169	3.021	-0.331	2.913	-0.223
54	1.832	1.688	0.144	1.379	0.453	1.488	0.344
55	1.505	1.719	-0.214	1.653	-0.148	1.802	-0.297

For external validation, activity of each molecule in the test set was predicted using the model generated from the training set. The pred_r^2 value is calculated as follows:

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

where y_i, and $\hat{y}_i$ are the actual and predicted activities of the i^{th} molecule in the test set, respectively, and y_{mean} is the average activity of all molecules in the training set.

Partial least squares regression (PLS) is a generalisation of regression, which can handle data with strongly correlated and/or noisy or numerous X-variables. It gives a reduced solution, which is statistically more robust than MLR. Cross-validation is a practical and reliable method for testing this significance[20-21].

RESULTS AND DISCUSSION

QSAR study was explored to investigate the structure–activity relationship of fifty-five compounds with distinguishing organic fragments acting as angiotensin II AT_1 receptor. The nature of models in a QSAR study is expressed by its fitting the data points through regression and making predictions of an isolated dataset. The partial least squares regression evaluation prompted the choice of four descriptors, which were eventually used to amassed a regression model for calculating pIC_{50} of AT_1 receptor within the chemical space of the model. Partial least squares regression equation developed was as follows:

pIC_{50}=0.3863(±0.0893) SdsCHE-index +0.1886 (±0.043) $SsCH_3E$-index+0.0488(±0.0082) T_2_Cl_1 - 0.4761(±0.0093) chi6chain

$N_{training}$ = 40, N_{test}= 15 Degree of freedom = 26, r^2= 0.8653, q^2= 0.7407, F test = 65.713, r^2_se = 0.3980, q^2_se = 0.3318, pred_r^2 = 0.7981, pred_r^2se = 0.4873

where, $N_{training}$ is the number of inhibitors in the training set, N_{test} is the number of inhibitors in the test set. The generated QSAR model was selected on the basis of various statistical parameters such as squared correlation co-efficient (r^2), which is relative measure of quality of fit; Fischer's value (F test) which represents F-ratio between the variance of calculated and observed activity; standard error (r2_se) representing absolute measure of quality of fit, and cross-validated square correlation co-efficient (q^2), standard error of cross-validated square correlation co-efficient (q2_se), predicted squared regression (pred_r2) and standard error of predicted squared regression (pred_r^2se) to estimate the predictive potential of the models, respectively. The generated model-1 showed a good correlation coefficient of 0.8653 and explains 86 % variance in biological activity and a very good prediction coefficient of the test set of 0. 7981. The model shows an internal predictive power (q^2 = 0.7407) of 79 % and a predictivity for the external test set (pred_r^2 = 0.79819) of about 79.81%. The F test value of 65.713 shows the overall statistical significance level for 99.99 % of the model, which means the probability of failure for the model is 1 in 10,000. The plot of actual versus predicted activity for the training and test sets of compounds in

both the cases is represented in Fig.1 (a). The predicted activities of the compounds by the above model are shown in Table III.

An estate contribution descriptor SdsCHE-index, which represents electro-topological indices for number of -CH group connected with one single bond, is inversely proportional to the activity. SdsCHE-index, indices for a number of -CH groups is connected with one single bond, in a molecule, indicating that the increase in molecular -CH led to increses the activity. In this group, a combination of all descriptors significantly enhanced the biological activity. The next descriptor, $SsCH_3E$-index, which represents electro-topological indices for number of eCH_3 group connected with one single bond, revealed the increase of activity with the presence of methyl group, such as compounds 6, 10, and 36 at the R2 position. The data suggests that methyl groups at the position of R2 of the ring are favourable for activity. The next descriptor, chi6chain, which is directly proportional to the activity, reveals that the increase in number of six-member rings and decrease in the branching on the six-member rings are favourable for the biological activity. As a positive contributing (~15 %) descriptor, T_2_Cl_1 [number of double-bonded atoms separated from the chlorine atom by single bonds] - suggests that the presence of substituents with chlorine at the R_2 position will lead to an enhance activity. The positive coefficient T_2_Cl_1 descriptor suggests that activity of compounds may be increased by increasing the number of chlorine atoms present in the nucleus (compounds 3, 7, 11, 27, 30 and 31 at R2 position). The above model-1 is validated by predicting the biological activities of the training and test molecules, as indicated in Table III. Correlation matrix of the selected descriptors that were reported in model 1 are presented in Table IV.

Table IV: Correlation matrix QSAR model 1

Parameter	SdsCHE-index	$SsCH_3E$-index	T_2_Cl_1	chi6chain
SdsCHE-index	1.0000			
$SsCH_3E$-index	0.0381	1.0000		
T_2_Cl_1	0.1752	0.0582	1.0000	
chi6chain	0.0427	0.2653	0.0631	1.0000

pIC_{50}=-0.0569(±0.0158) T_C_O_1+0.03487(±0.0056) SsCIE-index +0.1876 (±0.0042) Sulfurs Count

$N_{training}$ = 40, N_{test}= 15 Degree of freedom = 26, r^2= 0.7654, q^2= 0.6988, F test = 37.265, r^2_se = 0.3574, q^2_se = 0.2267, pred_r^2 = 0.7065, pred_r^2se = 0.3219

The model 2 shows correlation coefficient (r^2) 0.7654 and cross validated correlation coefficient (q^2) of 0.6988. Baumann's alignment descriptor has a negative contribution T_C_O_1 and showed count of number of carbon atoms (single double or triple bonded) separated from any oxygen atom (single or double bonded) by 1 bond distance in a molecule and has a detrimental effect on the activity. The next SsCIE-index descriptor [electro-topological state indices for number of chlorine atom connected with one single bond] shows that the electron-withdrawing chlorine atom on moiety group at R2 position is essential for the activity. Sulfurs count signifies number of sulphur atoms in a compound contributed negatively for towards the activity of structures. QSAR analysis of activity of moiety inferred that the substitutions of bulkier group at R2 position are favourable. The above model-2 is validated by predicting the biological activities of the training and test molecules, as indicated in Table III. The plot of actual versus predicted activity for the training and test sets of compounds in both the cases is represented in Fig.1 (b).

pIC_{50}=0.6265(±0.0214) Polar surface area excluding P and S +0.1653(±0.0518) SssNHcount +0.1884 (±0.0362) $SsCH_3E$ –index

$N_{training}$ = 40, N_{test}= 15 Degree of freedom = 26, r^2= 0.7061, q^2= 0.6649, F test = 22.654, r^2_se = 0.3574, q^2_se = 0.2267, pred_r^2 = 0. 6578, pred_r^2se = 0.3219

Model -3 shows good squared correlation coefficient (r^2) of 0.7061 explains 70 % variation in biological activity, being explained by the equation. This is associated with a low value of standard error of estimate, s, of 0.452. The equation is found to be highly statistically significant with F-test value of 22.654, critical F-test value at 99.9 % confidence. The model, when validated using leave one out method, showed good internal predictivity with the q^2 value being 0.6649, indicating good predictivity of the model. Model 3 shows the positive contribution of SssNHcount, i.e. electro topological state indices for the number of -NH groups connected with two single bonds descriptor is $SsCH_3E$ index electrotopological indice for number of methyl group connected with single bond and is inversely proportional to the activity. Positive contribution is augmented by adding methyl group in R2 position of moiety of the molecule having a detrimental effect on the activity. It reveals that the hydrophilic group on ring is essential for interaction with the receptor. The descriptor polar surface area excluding P and S were found to contribute more significantly to the activity, as indicated by their higher coefficients in the equation. The descriptor polar surface area excluding P and S signifies

that total polar surface area excluding phosphorous and sulphur plays an important role in detrimental effect on the activity. This suggests that substituents such as –OH, $–NO_2$, $-OCH_3$ and –COOH would increase the activity[22]. The above model-3 is validated by predicting the biological activities of the training and test molecules, as indicated in Table III. The plot of actual versus predicted activity for the training and test sets of compounds in both the cases represented in Fig.1 (c).

CONCLUSION

The above study leads to the development of statistically significant QSAR model, which allows understanding of the molecular properties that play an important role in governing the variation in the activities. The best model revealed the presence of SdsCHE-index, SsCH3E-index, T_2_Cl_1 and chi6chain that favour the activity in analogues. QSAR studies revealed that presence of chlorine, methyl, methoxy, hydroxyl groups on triazolinone moiety favours improvement in the activity. The present study may prove to be helpful in development and optimization for newly designed angiotensin II AT1 receptor.

ACKNOWLEDGMENTS

The authors are thankful to V-Life Sciences Technologies, India for providing trial version of the software.

REFERENCES

1. Hernández-Hernández R., Sosa-Canache B., Velasco M., Armas-Hernández M.J., Armas-Padilla M.C. and Cammarata R.: Angiotensin II receptor antagonists role in arterial hypertension. **J. Hum. Hypertens.,** 2002, 16(1), S93-9.
2. Maggioni A.P.: Efficacy of Angiotensin receptor blockers in cardiovascular disease. **Cardiovasc Drugs Ther**., 2006, 20(4), 295-308.
3. Cernes R., Mashavi M. and Zimlichman R.: Differential clinical profile of candesartan compared to other angiotensin receptor blockers. **Vasc. Health. Risk. Manag.,** 2011,7, 749-759.
4. Vallotton M. B.: The renin angiotensin system. **Trend. Pharmacol. Sci.,** 1987 8, 69-74.
5. Ondetti M. A. and Cushman D.W.: Inhibition of the renin angiotensin system: a new approach to the therapy of hypertension. **J. Med. Chem.,** 1981, 24, 355–361.
6. Nahmias C. and Strosberg A. D.: The angiotensin AT_2 receptor: searching for signal-transduction pathways and physiological function. **Trends. Pharmacol. Sci.,** 1995, 16, 223-225.
7. Weber M. A.: The angiotensin II receptor blockers: opportunities across the spectrum of cardiovascular disease. **Rev. Cardiovasc. Med**., 2002, 3(4), 183-191.
8. Sadashiva S. K., Hamiyet U., Jacqueline R. K., Kalyan C. T., Satoru E., Patrick M. L. V. and Walter G. T.: International Union of Basic and Clinical Pharmacology. XCIX. Angiotensin Receptors: Interpreters of Pathophysiological Angiotensinergic Stimuli. **Pharmacol. Rev**., 2015, 67(4), 754–819.
9. Hansch C. and Fujita T.: p-σ-ϖ Analysis. A Method for the Correlation of Biological Activity and Chemical Structure**. J. Am. Chem. Soc.,** 1964, 86, 1616-1626.
10. Chou K.C.: Structural bioinformatics and its impact to biomedical science**. Curr. Med. Chem.,** 2004, 11(16), 2105–2134.
11. Sharma M.C., Kohli D.V. and Sharma S.: Molecular Modeling Studies of Substituted 2,4,5-Trisubstituted Triazolinones Aryl and Nonaryl Derivatives as angiotensin II AT_1 receptor antagonists. **J. Chem.,** 2013 doi. org/10.1155/2013/427181
12. Chang L.L., Ashton W.T., Flanagan K.L., Strelitz R.A., Maccoss M., Greenlee W.J., Chang R.S., Lotti V.J, Faust K.A., Chen T.B., Bunting P., Zíngaro G.J., Kivlighn S.D. and Siegl P. K. S.:Triazolinones as nonpeptide angiotensin II antagonists. 1. Synthesis and evaluation of potent 2,4,5-trisubstituted triazolinones. **J. Med. Chem.,** 1993, 36(17), 2558-2568.
13. VLIFE MDS Molecular Design Suite, VLife Sciences Technologies Pvt. Ltd., Pune, India, 2004.
14. Halgren T.A. and Nachbar R.: Merck molecular force field. IV. Conformational energies and geometries for MMFF94. **J. Comput. Chem.,** 1996, 17, 587-615.
15. Golbraikh A. and Tropsha A.: Predictive QSAR modeling based on diversity sampling of experimental datasets for the training and test set selection. **J. Comput. Aided. Mol. Des.,** 2002, 16, 357-369.
16. Baumann K.: An alignment-independent versatile structure descriptor for QSAR and QSPR based on the distribution of molecular features. **J. Chem. Inf. Comput. Sci.,** 2002, 42, 26-35.
17. Veerasamy R., Rajak H., Jain A., Sivadasan S., Varghese C.P. and Agrawal R.K.: Validation of QSAR models-strategies and importance. **Int. J. Drug. Des. Discov.,** 2011, 3,511-519.
18. Golbraikh A. and Tropsha A: Beware of q^2! **J. Mol. Graph. Model.,** 2002, 20(4),269–276.
19. Cramer R.D., Patterson D.E. and Bunce J.D.: Comparative Molecular Field Analysis (CoMFA). 1. Effect of shape on binding of steroids to carrier proteins. **J. Am. Chem.Soc.,** 1988, 110, 5959-5967.
20. Wold S.: in PLS for Multivariate Linear Modeling, H. van de Waterbeemd, ed., VCH, Weinheim, 1995, 195–218.
21. Sahu N.K., Shahi S., Sharma M.C. and Kohli D.V.: QSAR studies on imidazopyridazine derivatives as PfPK7 inhibitors. **Mol. Sim**., 2011, 37(9), 752–765.
22. Parate A. and Chaturvedi S.C: Structural insights for 3*H*-1, -2, -4 triazolinones as angiotensin II receptor antagonists using QSAR techniques. **Med. Chem. Res.,** 2010, 19, 375–391.