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Original Article

Predictive Modeling of Phenylpiperazine Derivatives for Renin Inhibition

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Abstract

The renin–angiotensin–aldosterone system is the well-established endocrine system having significant role in preserving hemodynamic stability. Renin is secreted from the juxtaglomerular cells of the kidney. Phenylpiperazine derivatives have been reported as human renin inhibitor. To do the study, a predictive QSAR modeling for 27 phenylpiperazine derivatives as renin enzyme inhibitors was used. The IC_{50} values for purified human renin were taken as biological activity. Physicochemical properties were calculated on Dragon software, version 5.5. Hierarchical Multiple Regression was performed to obtain quantitative structure-activity relationship model which again validated internally and externally. The selected best QSAR model had the correlation coefficient (R^2) of 0.843, and predicted correlation coefficient (R^2pred) of 0.867. The predictive ability of the selected model was established by leaving one-out cross-validation. Different Rm2 matrices were also calculated to validate the model externally. The quantitative structure activity relationship study indicates that CIC2, BIC2, and R7v descriptors have a very important role in renin enzyme and ligand interaction. The developed model can be applied to design new effective renin enzyme inhibitors.

Keywords: Complementary Information Content index, GATEWAY, Juxtaglomerular cell tumor, Novel descriptors For '*Renin'* binding, *'Phenylpiperazine'*, QSAR, Treatment of hypertension, Wilms' tumor

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1. Introduction

The renin–angiotensin–aldosterone system (RAAS) is a hormone system involved in maintaining hemodynamic stability in response to the loss of blood, salt, and water. In the RAAS pathway, the juxtaglomerular cells of the kidney secrete the rate-limiting

enzyme renin. It acts on the circulating precursor angiotensinogen to generate angiotensin-I. Angiotensin-I converted to angiotensin-II. Angiotensin-II is a potent vaso-active peptide that causes arterioles to constrict, resulting in increased arterial blood pressure [1-3]. The peptides were first synthetic molecules of renin inhibitors like zanikiren, remikiren. These drugs have poor oral bioavailability, quick elimination, low effectiveness, and high cost of synthesis process.

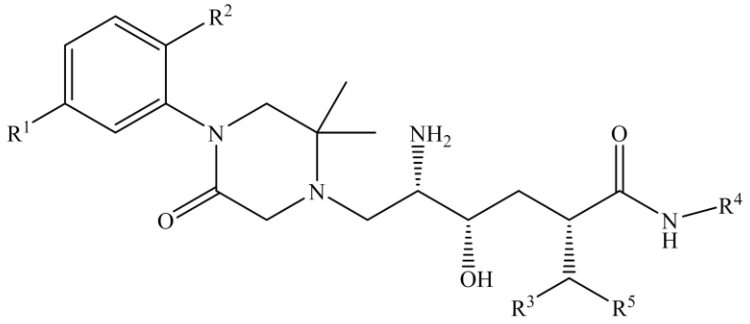
Novartis in collaboration with the biotech company Speedel developed Aliskiren, the first oral direct renin inhibitor. Direct renin inhibitors have advantage to offer better kidney and heart protection and have fewer adverse events than ACE inhibitors and AT1 blockers [4-12].

A phenylpiperazine derivative, SGB-1534 was found to have antihypertensive effects on rats [13]. Hence renin offers the potential improved targeting of the mechanisms that underpin hypertension and cardiovascular disease [14]. A very accurate QSAR study on piperazine and keto piperazine derivative renin inhibitors has been reported [15]. Recently lead optimization of 5-amino-6-(2, 2-dimethyl-5-oxo-4-phenylpiperazin-1-yl)-4-hydroxyhexanamides was carried out which lead to discovery of DS-8108b, an orally active renin inhibitor [16]. Herein, we report a quantitative structure-activity relationship (QSAR) study to investigate the structural features of 27 phenylpiperazine derivatives required for renin inhibiting activity.

2. Materials and Methods

27 structures phenylpiperazine derivatives (Table 1) selected randomly were used to build a QSAR model [16]. IC_{50} (nM) values were converted to negative logarithmic (M) values for the statistical studies. The structures were split randomly in to the training set (20 structures) and test set (7 structures). The structures were constructed and transformed to 3-dimentional using Chem Office 2004, Version 8.0 [17]. The energy minimization using molecular mechanics-2 (MM2) till the root mean square (RMS) gradient value attains the value lesser than 0.100 kcal/mol Å. The energy minimized molecules were again subjected to re-optimization using the AM1 procedure of MOPAC (Molecular Orbital Package) module until the RMS gradient reached a value lesser than 0.0001kcal/mol Å [17]. Total 3224 molecular descriptors were calculated on the DRAGON Software, version 5.5 (Table 2) [18].VALSTAT program was used to develop Hierarchical Multiple Regression models [19]. The QSAR models were validated internally by "Leave-one-out (LOO)" method. Various statistical parameters such as correlation coefficient (R), determination coefficient (R^2), and adjusted R^2 were used. The cross-validated squared correlation coefficient (Q^2), standard deviation of prediction (S_{PRESS}) and standard deviation of error of prediction (S_{DEP}) were calculated to estimate the predictive ability the each model. To confirm the robustness and utility of QSAR models, the bootstrapping square correlation coefficient (R^2_{bt}) was calculated. The F Value

Table 1. IUPAC name and experimental data of phenylpiperazine based Purified Human renin enzyme inhibitors.



Sr.No.	Structure `s IUPAC Name	Purified human renin IC_{50}(M)
1.	(2S,4S,5S)-5-amino-6-(4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl)-4-hydroxy-2-isopropyl-N-neopentylhexanamide	9.000
2.	(2S,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]-4-hydroxy-N-isobutyl-2isopropylhexanamide	8.854
3.	(2R,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]-N-(2,2-dimethylpropyl)-4-hydroxy-2methylhexanamide	9.000
4.	(2R,4S,5S)-5-Amino-N-(2,2-dimethylpropyl)-6-[4-(5-fluoro-2-methylphenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]-4-hydroxy-2-methylhexanamide	8.959
5.	(2S,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]-4-hydroxy-N-(3-hydroxy-2,2dimethylpropyl)-2-isopropylhexanamide	8.770
6.	(2R,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]-2-ethyl-4-hydroxy-N-(3-hydroxy-2,2dimethylpropyl)hexanamide	8.796
7.	(2S,4S,5S)-5-Amino-N-(3-amino-2,2-dimethyl-3-oxopropyl)-6-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]-4-hydroxy-2-isopropylhexanamide	8.854
8.	Methyl 3-{[(2S,4S,5S)-5-amino-6-[4-(2-chlorophenyl)2,2-dimethyl-5-oxopiperazin-1-yl]-4-hydroxy-2isopropylhexanoyl]amino}-2,2-dimethylpropanoate	8.745
9.	(2S,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl5-oxopiperazin-1-yl]-4-hydroxy-N-(trans-4hydroxycyclohexyl)-2-isopropylhexanamide	8.854
10.	(2S,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]-4-hydroxy-2-isopropyl-N-phenylhexanamide	8.854
11.	(2S,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl5-oxopiperazin-1-yl]-4-hydroxy-2-isopropyl-N-(pyridin-2yl)hexanamide	8.745
12.	(2S,4S,5S)-5-Amino-6-[4-(5-fluoro-2-methylphenyl)-2,2dimethyl-5-oxopiperazin-1-yl]-4-hydroxy-2-isopropyl-N(pyridin-3-yl)hexanamide	8.620
13.	(2S,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2dimethyl-5-oxopiperazin-1-yl]-4-hydroxy-2-isopropyl-N(pyridin-4-yl)hexanamide	8.796
14.	(2R,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl5-oxopiperazin-1-yl]-2-ethyl-N-(4-fluorophenyl)-4hydroxyhexanamide	8.796

15.	(2S,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl5-oxopiperazin-1-yl]-N-(3,4-difluorophenyl)-4-hydroxy-2isopropylhexanamide	8.721
16.	(2S,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl5-oxopiperazin-1-yl]-N-(2,4-difluorophenyl)-4-hydroxy-2isopropylhexanamide	8.699
17.	(2R,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]-2-ethyl-N-[3-ethyl-3(hydroxymethyl)pentyl]-4-hydroxyhexanamide	9.000
18.	(2R,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]-2-ethyl-4-hydroxy-N-{2-[1(hydroxymethyl)cyclopentyl]ethyl}hexanamide	8.959
19.	(2R,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]-2-ethyl-4-hydroxy-N-{2-[1(hydroxymethyl)cyclohexyl]ethyl}hexanamide	8.959
20.	(2S,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl5-oxopiperazin-1-yl]-4-hydroxy-N-[(2s,5s)-5hydroxyadamantan-2-yl]-2-isopropylhexanamide	8.886
21.	(2R,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl5-oxopiperazin-1-yl]-4-hydroxy-N-[(2s,5s)-5hydroxyadamantan-2-yl]-2-methylhexanamide	8.959
22.	(2S,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl5-oxopiperazin-1-yl]-4-hydroxy-N-(3-hydroxyadamantan-1yl)-2-isopropylhexanamide	8.699
23.	trans-4-({(2R,4S,5S)-5-Amino-6-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]-2-ethyl-4-hydroxyhexanoyl}amino)adamantane-1-carboxamide	8.886
24.	(2S,4S,5S)-5-Amino-6-[4-(2-chloro-5-fluorophenyl)-2,2dimethyl-5-oxopiperazin-1-yl]-4-hydroxy-N-[(2s,5s)-5hydroxyadamantan-2-yl]-2-isopropylhexanamide	8.721
25.	(2R,4S,5S)-5-Amino-6-[4-(2-chloro-5-fluorophenyl)-2,2dimethyl-5-oxopiperazin-1-yl]-2-ethyl-4-hydroxy-N-[(2s,5s)-5hydroxyadamantan-2-yl]hexanamide	8.854
26.	(2S,4S,5S)-5-Amino-6-[4-(5-fluoro-2-methylphenyl)-2,2dimethyl-5-oxopiperazin-1-yl]-4-hydroxy-N-[(2s,5s)-5hydroxyadamantan-2-yl]-2-isopropylhexanamide	8.770
27.	(2R,4S,5S)-5-Amino-6-[4-(5-fluoro-2-methylphenyl)-2,2dimethyl-5-oxopiperazin-1-yl]-2-ethyl-4-hydroxy-N-[(2s,5s)-5-hydroxyadamantan-2-yl]hexanamide	8.796

or F ratio is used to decide whether the model as a whole has statistically significant predictive capability, that is, whether the regression sum of squares is big enough, considering the number of variables needed to achieve it. F is the ratio of the Model Mean Square to the Error Mean Square. The predictive R^2 (R^2_{pred}) was calculated on applying the derived model on test set compounds. To further validate the model on stringent condition, various r_m^2 metrics were also calculated [20, 21].

To detect outliers the Z score method was adopted. The Z score is the absolute difference between the value of the model and the activity field, divided by the square root of the mean square error of the data set. Any compound having Z score greater than 2.5, during generation of a particular QSAR model, is measured as an outlier.

Table 2. Descriptors Values of compounds.

Sr. No.	[a]CIC2	[b]BIC2	[c]R7v
1	1.747	0.709	0.406
2	1.629	0.724	0.389
3	1.624	0.722	0.353
4	1.552	0.737	0.354
5	1.520	0.745	0.401
6	1.415	0.759	0.377
7	1.530	0.742	0.399
8	1.492	0.750	0.386
9	1.471	0.752	0.381
10	1.499	0.735	0.420
11	1.231	0.776	0.397
12	1.100	0.799	0.391
13	1.219	0.778	0.385
14	1.236	0.773	0.384
15	1.259	0.772	0.420
16	1.232	0.777	0.426
17	1.620	0.735	0.337
18	1.504	0.749	0.338
19	1.609	0.736	0.337
20	1.609	0.736	0.337
21	1.420	0.758	0.347
22	1.576	0.739	0.429
23	1.472	0.753	0.340
24	1.489	0.752	0.392
25	1.430	0.759	0.369
26	1.492	0.754	0.391
27	1.435	0.761	0.363

[a]CIC2 Complementary Information Content index (neighborhood symmetry of 2-order), [b]BIC2 Bond Information Content index (neighborhood symmetry of 2-order, [c]R7v R autocorrelation of lag 7 / weighted by van der Waals volume.

3. Result and Discussion

A QSAR model for 27 phenylpiperazine derivatives was developed to explain the correlation between physical and chemical properties. Different Hierarchical Multiple Regression equations were obtained and the best statistically significant equation was discussed here.

BA= [19.4596(± 4.9528)] +CIC2 [-1.04662(± 0.662765)] +BIC2 [-10.7874(± 5.09831)] +R7v [-2.61234(± 0.852524)]

The statistical data for this equation are shown in (Table 3**)**.The above model was considered as the best model due to its overall predictivity. The inter-correlation among descriptors is found high which could be due to synergistic interaction of descriptors (Table

Table 3. Statistical values and Parameters for QSAR Model[#].

Parameters		Statistical values
N Train		20
N test		7
NV		3
R		0.918
R^2		0.843
Adjusted R^2		0.814
Variance		0.002
Std		0.044
F		28.570
R^2_{bt}		0.850
Chance		0.001
Q^2		0.738
SPRESS		0.056
SDEP		0.051
R^2pred		0.867
r_m^2 (Loo)	**rm2 value**	0.716
	Reverse rm2	0.569
	Average rm2	0.642
	Delta rm2	0.147
r_m^2 (Predicated)	**rm2 value**	0.869
	Reverse rm2	0.748
	Average rm2	0.809
	Delta rm2	0.121
r_m^2 (Overall)	**rm2 value**	0.764
	Reverse rm2	0.627
	Average rm2	0.695
	Delta rm2	0.137

#N Train= number of training set, N Test= number of test set, NV= number of variables, R= coefficient of correlation, R^2= squared correlation coefficient, Std= standard deviation of estimation, F= Fischer's value, R^2_{bt}= bootstrapping square correlation coefficient, Q^2=cross-validated squared correlation coefficient, SPRESS= predictive residual sum of square, S_{DEP} = standard error of prediction. R^2 = predicted coefficient of correlation

Table 4. Inter-correlation of structural descriptors and their correlation with the activity.

Parameters	$logIC_{50}$(M)	CIC2	BIC2	R7v
$logIC_{50}$(M)	1			
CIC2	0.675	1		
BIC2	0.697	0.970	1	
R7v	0.668	0.301	0.201	1

4). In addition, the multi co-linearity resulted from use correlated descriptors is not problematic as it is frequently assumed. Several literatures present highly significant

Table 5. Calculated and predicted biological activity of the training set.

Compound no.	Observed activity	Calculated activity	Predicted activity
1	9.00	8.922	8.88
2	8.85	8.928	8.95
3	8.96	8.960	8.96
4	8.77	8.785	8.79
6	8.85	8.812	8.81
7	8.74	8.799	8.80
9	8.85	8.865	8.87
10	8.74	8.763	8.77
11	8.80	8.785	8.78
13	8.72	8.717	8.72
14	8.70	8.676	8.67
16	9.00	8.955	8.94
17	8.96	8.923	8.92
19	8.96	8.956	8.96
20	8.89	8.956	8.97
22	8.70	8.718	8.73
25	8.72	8.765	8.77
27	8.85	8.811	8.81

Table 6. Predicted biological activity of the test set.

Compound no.	Observed activity	Predicted activity
3	9.000	9.049
6	8.796	8.806
9	8.854	8.813
12	8.620	8.668
14	8.796	8.824
21	8.959	8.890
23	8.886	8.908

regression equations which involve the pairs of highly correlated, poorly performing single-parameter descriptors [22-25].

The model exhibits a superior correlation coefficient (R) of 0.918 among the descriptors CIC2 (Complementary Information Content index [neighborhood symmetry of 2-order]), BIC2 (Bond Information Content index (neighborhood symmetry of 2-order) R7v (R autocorrelation of lag 7 / weighted by van der Waals volume) and rennin binding affinity. The determination correlation (R^2) of 0.843 indicates 82.4 % of the variance in the biological activity. The R^2-adjusted is 0.814 which shows model accounts for 81.4 % of the total variability. The F value = 28.570 (level more than 95%) with a low standard deviation of estimation (0.044), manifest the precision of

the model. The model was found to be stable for usefulness of model for consequential predictions ($Q^2 > 0.6$). The model was said to be robust having the R^2_{bt} (0.850) near to conventional R^2 **(**0.843**).** The low values of the cross-validation parameters S_{PRESS} and S_{DEP} provide further support. The predicted R^2 value of the test sets compound was found to be 0.867. Average rm2 required to be > 0.5 & Delta rm2 to be < 0.2 for excellent predictive ability of the model [19, 20]. The observed, calculated and the predicted values of biological activity are tabulated in (Table 5) and (Table 6). The correlation between observed and LOO-predicted activity of the training and test set are shown in figure 1.

The developed regression model-3 discloses that the descriptors CIC2 Complementary Information Content index (neighborhood symmetry of 2-order), BIC2 Bond Information Content index (neighborhood symmetry of 2-order and R7v R autocorrelation of lag 7 / weighted by van der Waals volume. affect inversely to renin inhibitory activity. The CIC2 and BIC2 belong to multi-graph information content indices.

This indices of neighborhood symmetry (of 2-order) takes into account neighbor degree and edge multiplicity. The CIC2 descriptor represents the difference between the maximum possible complexity of a molecule and its real topological information. BIC2 represents the number of bonds counting bond orders which defines binding symmetry. Thus, higher values of parameters (that define binding and complementary symmetries) decide the decrease of biologic activity. That means decreased biologic activity is the implication of more asymmetrical molecular shape [26, 27]. The least potent compounds (Compound no. 12, 16 and 22) are having ring

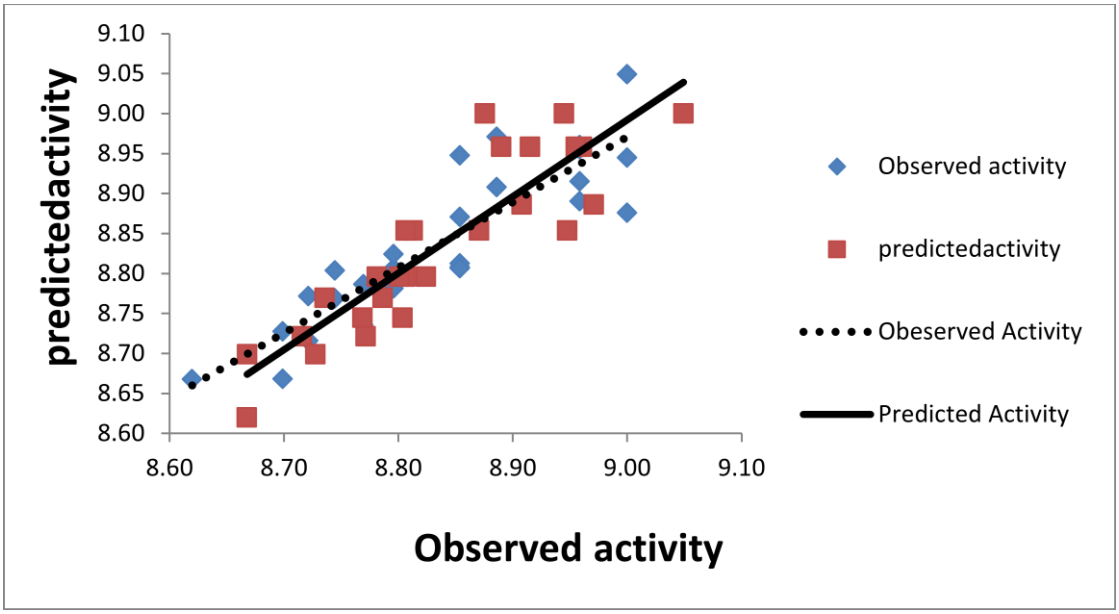
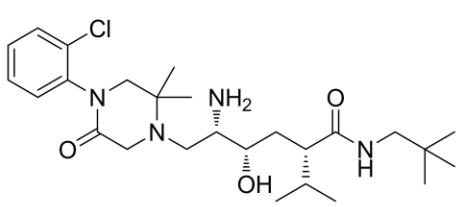


Figure 1. The correlation between observed and predicted activity of the training and test set.

Most potent compound 1,3,17



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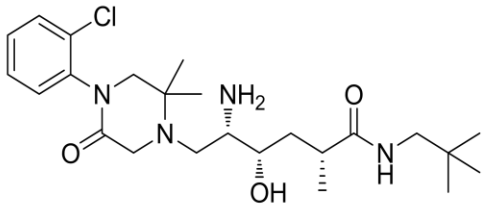

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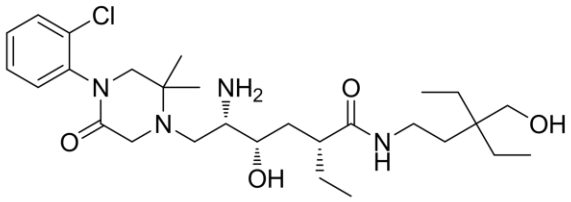

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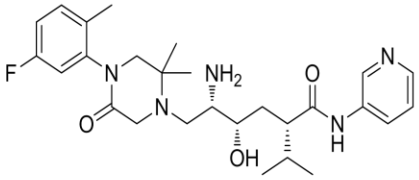
Least potent compound 12, 16, 22



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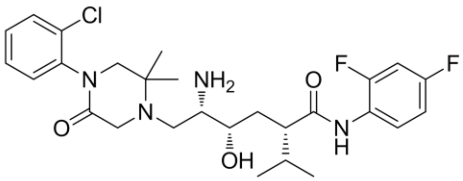
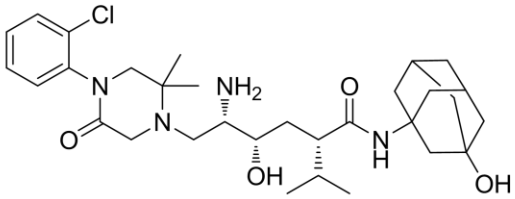


16



22

Figure 2. Most and Least Potent Compounds.

system at the amide nitrogen which makes molecules more symmetric. On other side, most potent compounds (compound no. 1, 3 and 17) are having aliphatic side chain at amide nitrogen which makes molecule less symmetric (Figure 2).

R7v belongs to GETAWAY descriptors which encode both the geometrical information and the topological information using different atomic weightings (atomic mass, polarizability, vander Waals volume, and electro negativity, together with unit weights).

GATEWAY descriptors are calculated based on spatial autocorrelation, encoding information on structural fragments and therefore appears to be particularly suitable for describing variations in congeneric molecular series [28]. There is a bulky ring system at amide nitrogen in least potent compounds (Compound no. 12, 16 and 22) that increase the vander Waals volume causing steric unfavorable condition. While most potent compounds (compound no. 1, 3 and 17) have less bulky open aliphatic chain having less vander Waals volume (Figure 2).

4. Conclusion

QSAR study was carried out to establish the quantitative effects structure of the molecules on their renin inhibiting activity. The model has been validated by the appropriate statistical parameters. The inverse relationship of descriptors CIC2, BIC2, and Rv7 revealed that more symmetric molecules have less potency. The presented study provides valuable evidences for development of newer effective renin inhibitors.

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