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Development and Validation of a Robust QSAR Model For Piperazine and Keto Piperazine Derivatives as Renin Inhibitors

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Abstract:

Background:

The renin is a key performer in the renin–angiotensin system, and it offers a resource for the beneficial action of hypertension and heart malfunction. The keto piperazine based renin inhibitors have shown greater potential and good biavaibility.

Objective:

To develop a highly efficient QSAR model for 80 piperazines and keto piperazines to predict renin enzyme inhibitory activity.

Methods:

The renin inhibitory activity (IC_{50}) was considered as biological activity. Dragon software, version 5.5 was used for calculation of physicochemical parameters. Sequential MLR (multiple linear regression) is carried out to create quantitative structure–activity relationship models, which were again evaluated in support of statistical significance and analytical capacity by inner and exterior validation.

Results:

The greatest QSAR model was a correlation coefficient (R^2) of 0.846, cross-validation correlation coefficient (Q^2) of 0.818 and, R^2 pred of 0.821. The leave one out cross validation method was used to assess the performance of the chosen model.

Conclusion:

The quantitative structure–activity relationship model suggests that the constitutional descriptors (Sv, nDB, nO) play a vital role in binding of ligands with renin enzyme. The information presented provides important structural insight in designing more potent renin enzyme inhibitors.

Keywords: Competitive balance, novel descriptors, piperazine and keto piperazine derivatives, renin, renin binding, robust QSAR.

INTRODUCTION

The renin–angiotensin–aldosterone system (RAAS) is a key controller of blood pressure; it has a reno-protective function and a very significant position in the vascular reaction to the damage [1]. Renin is aspartic protease, which consists of one of the four key classes of peptide cleave enzymes [2]. It is concealed by the nephron in feedback to reduce circulation level and blood pressure. Renin cleaves the substrate angiotensinogen to provide the stationary angiotensin-I. Angiotensin converting enzymes convert Angiotensin-I to the pro-hypertensive agent angiotensin receptor blockers. The renin is an input performer in the renin–angiotensin structure, and its operation offers a resource used for the beneficial action of hypertension and heart malfunction.

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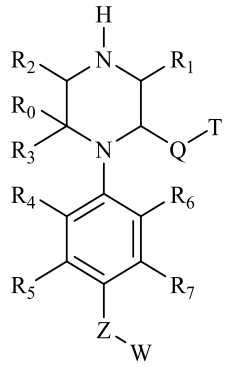
Renin hang-up is an eye-catching object for drug involvement due to its notable specificity intended for its substrate [3, 4]. The key man-made molecules were peptide or peptide-like renin inhibitors remikiren and zanikiren showing poor oral bioavailability, quick elimination, little efficiency, and high rate of chemical synthesis. Just utilizing the combination of drug design and crystallographic structure analysis led to the development of aliskiren, non-peptide orally effective inhibitor of human renin [5 - 9].

Pfizer pursued the task of designing the keto piperazine based renin inhibitors which have shown greater potential [10, 11]. More recently, a novel series of renin inhibitors based on the 3, 9-diazabicyclo nonene have been developed [12]. The piperazine and keto piperazine derivatives have been found to be potent, efficacious, oral and good bioavailable renin inhibitors [11, 13, 14]. In this study, novel quantitative structure–activity relationship models were built to illustrate the magnitude of the physicochemical properties intended for the piperazine and keto piperazine derivatives as renin inhibitors.

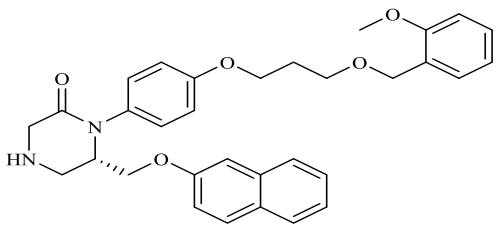
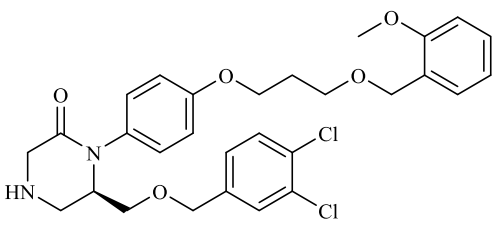
MATERIALS AND METHODS

A total of 80 piperazine and keto piperazine based renin inhibitors were included in Quantitative structure–activity relationship study as accounted in Table **1** [13]. IC_{50} (μM) values changed in logarithmic (M) values, which were used for the regression studies.

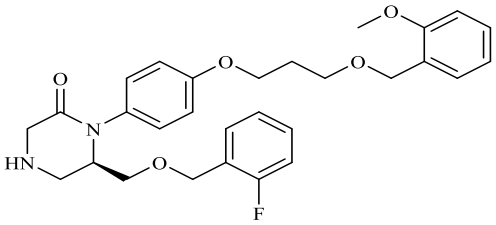
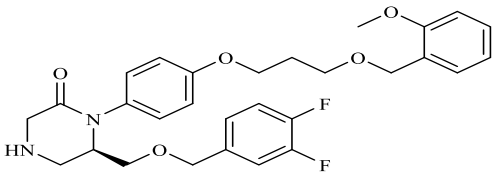
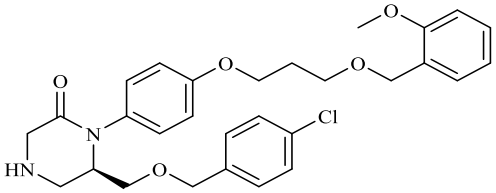
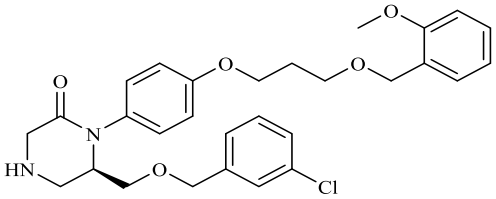
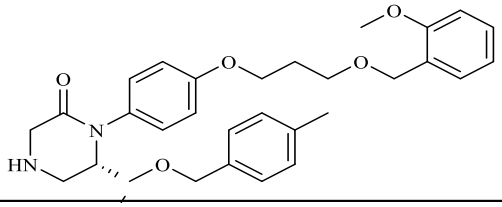
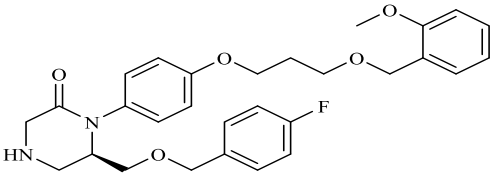
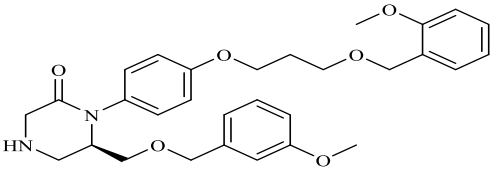
Table 1. Molecules 's Structures and Experimental values of piperazine and keto piperazine based renin enzyme inhibitors.



1 - 80

No.	Compound `s Structures	IC_{50}(μM) Experimental
1		0.066
2		0.181

(Table 1) contd.....

No.	Compound `s Structures	IC_{50}(µM) Experimental
3		0.225
4		0.246
5		0.295
6		0.325
7		0.337
8		0.454
9		0.612

(Table 1) contd.....

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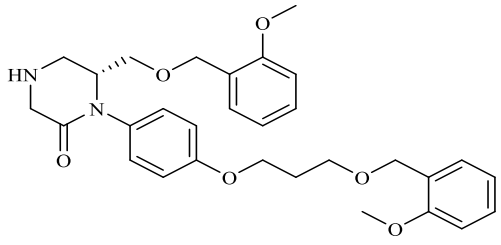
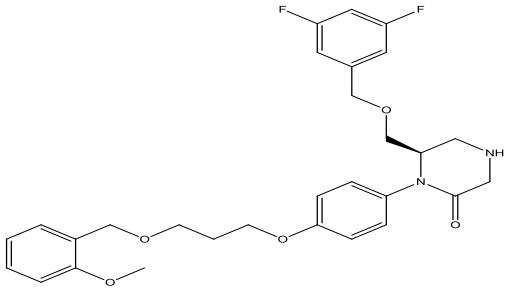
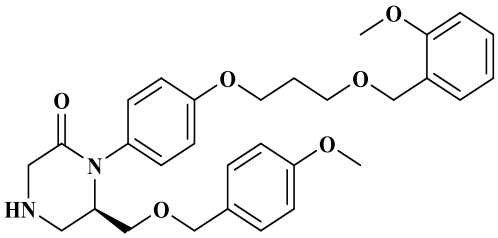
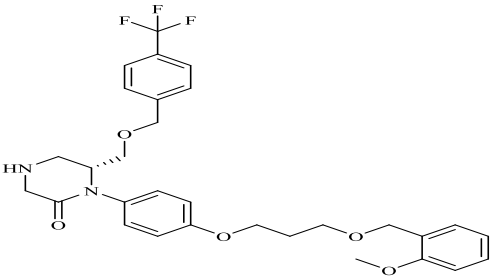
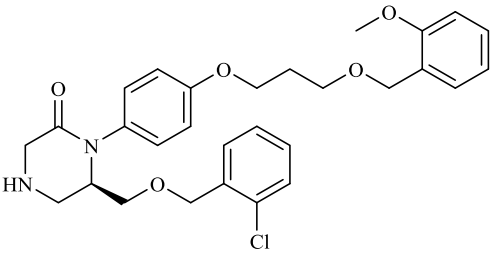
10		0.880
11		1.573
12		3.864
13		0.068
14		0.223

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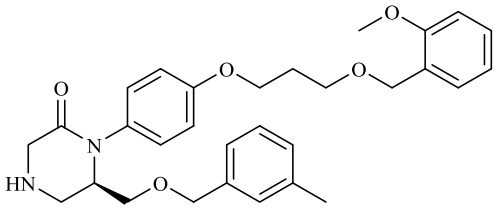
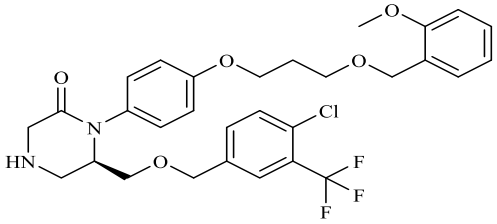
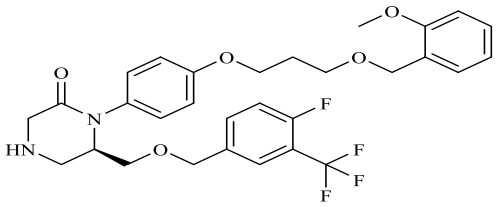
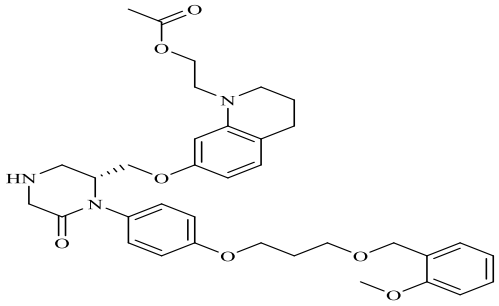
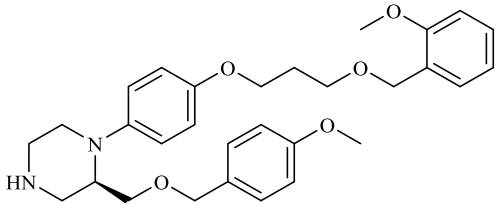
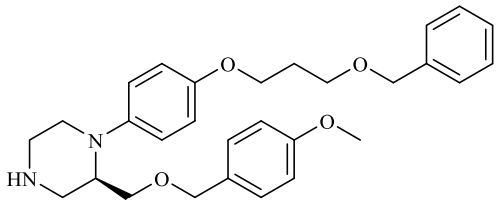
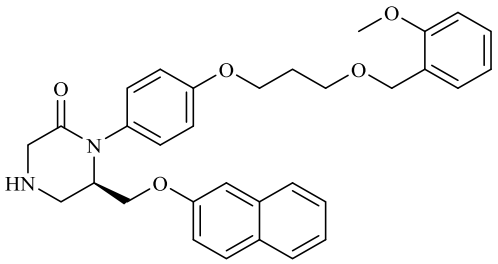
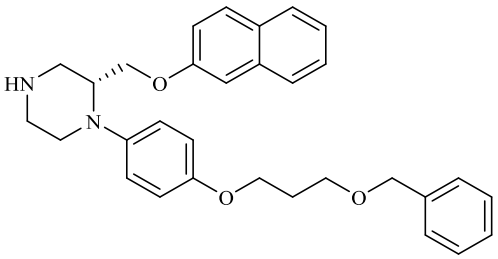
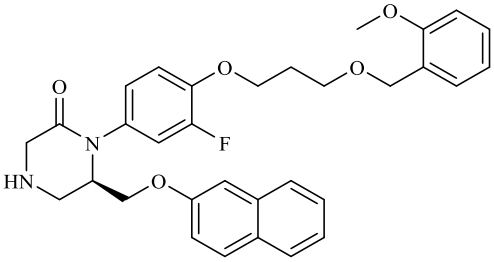
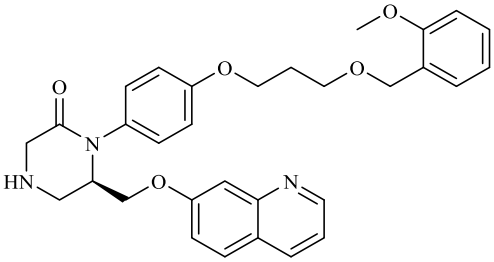
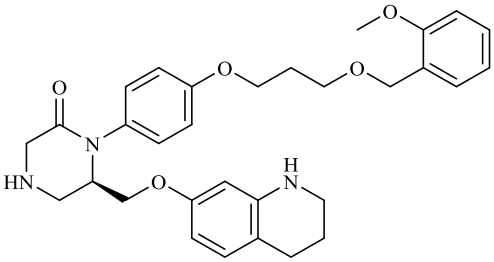
No.	Compound `s Structures	IC_{50}(µM) Experimental
15		0.372
16		0.107
17		0.132
18		0.00042
19		3.990
20		10.900

(Table 1) contd.....

No.	Compound `s Structures	IC_{50}(µM) Experimental
21		0.054
22		1.420
23		0.152
24		0.822
25		0.124

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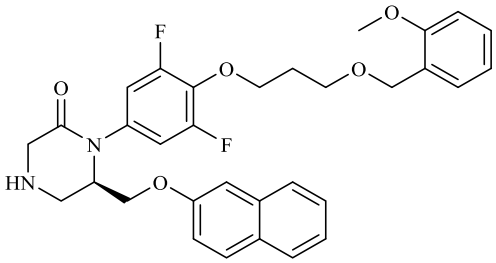
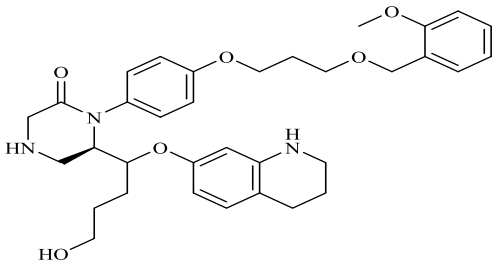
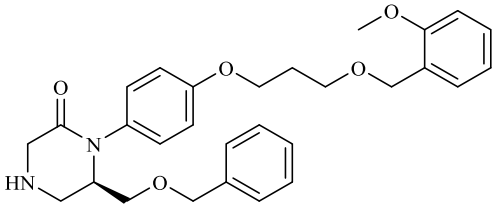
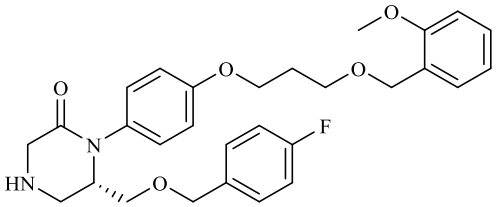
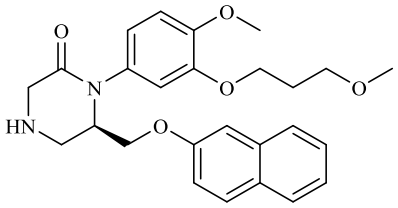
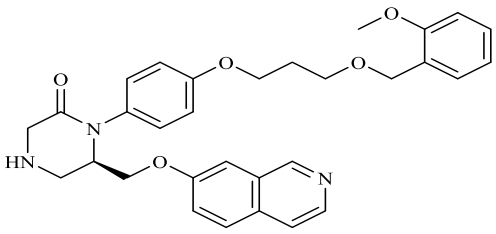
26		0.883
27		0.037
28		7.014
29		5.586
30		3.841
31		0.528

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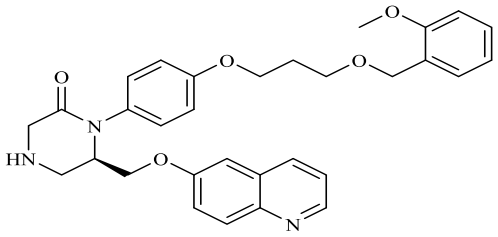
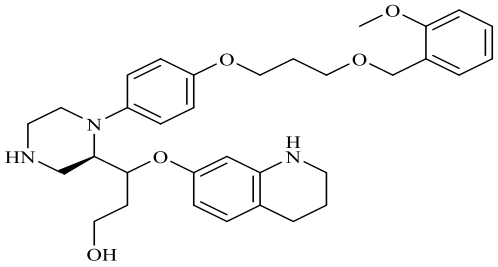
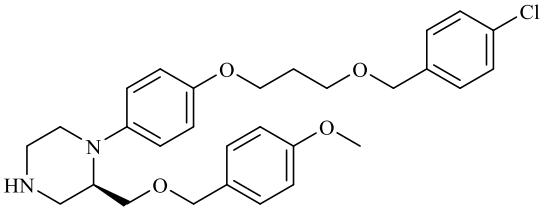
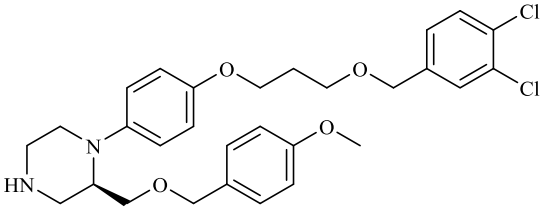
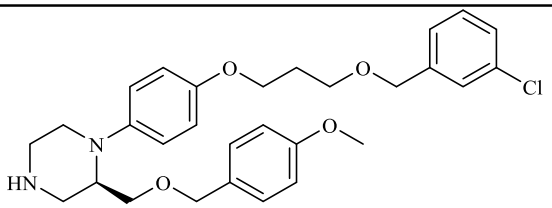
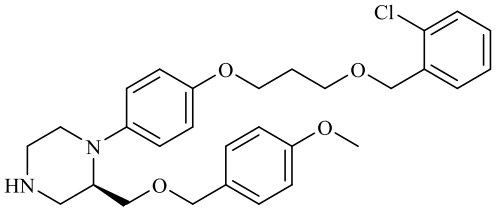
32		3.450
33		0.064
34		43.700
35		11.500
36		5.040
37		15.900

(Table 1) contd.....

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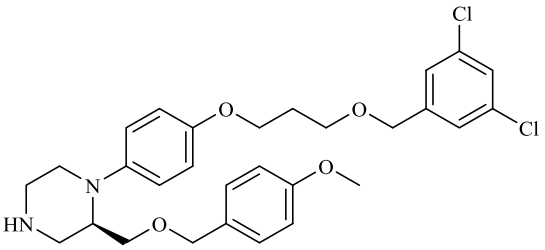
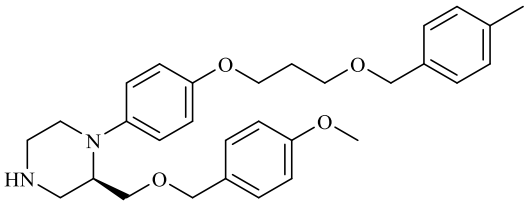
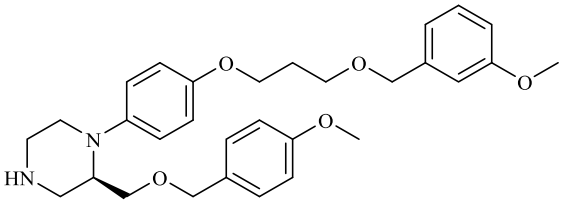
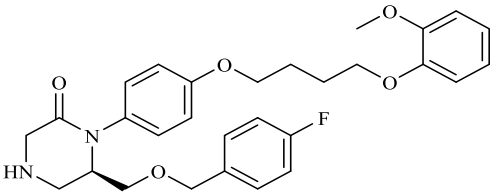
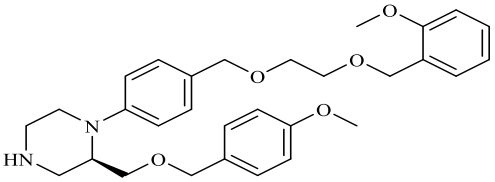
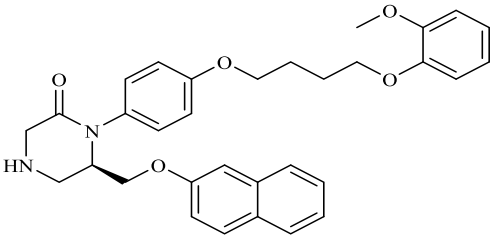
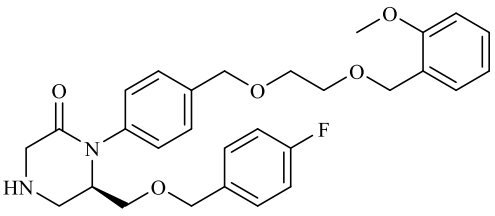
38		4.340
39		60.200
40		15.600
41		3.840
42		30.500
43		1.729
44		4.090

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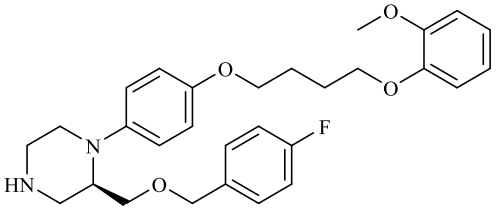
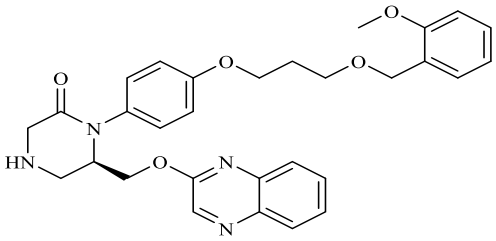
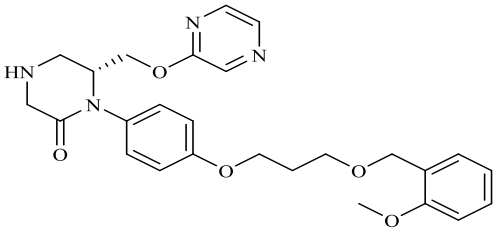
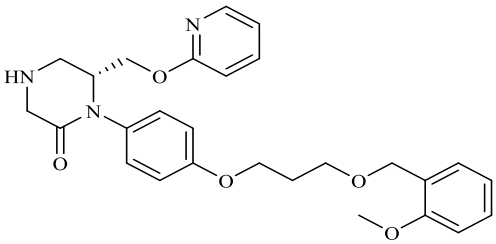
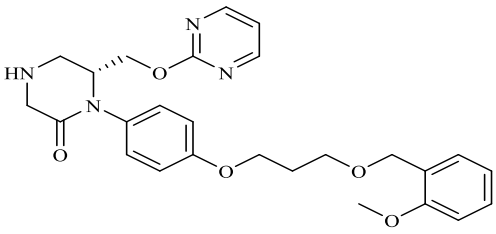
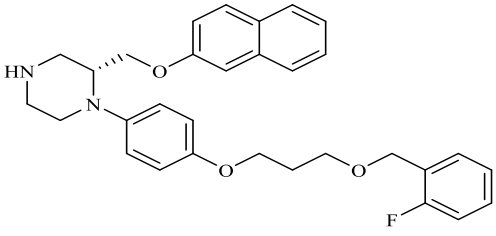
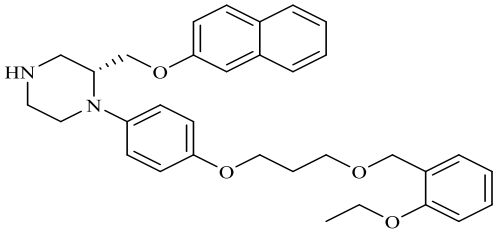
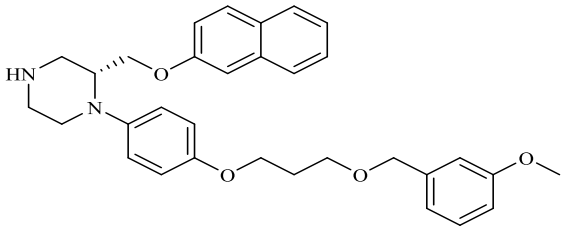
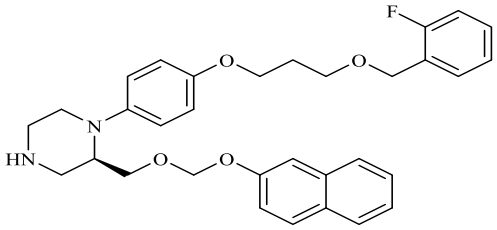
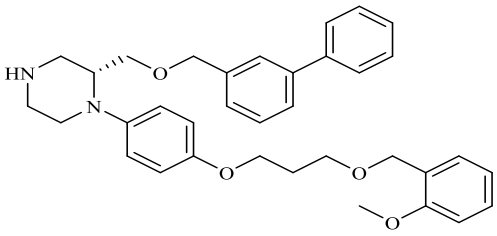
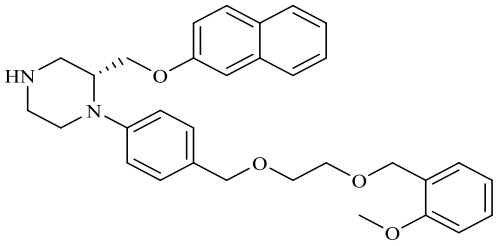
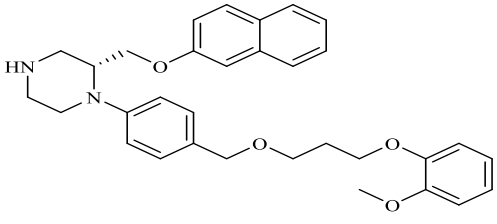
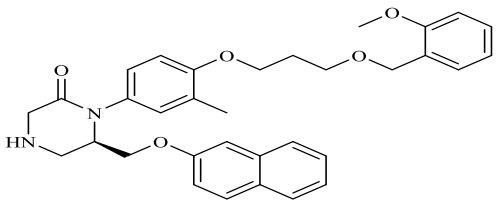
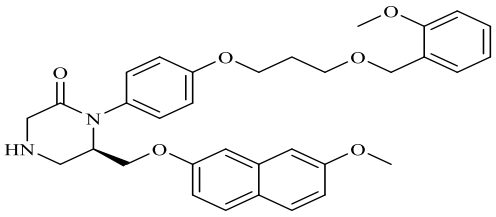
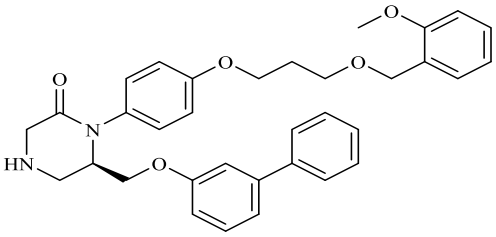
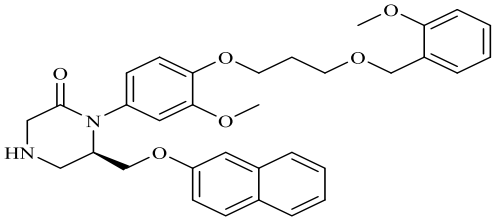
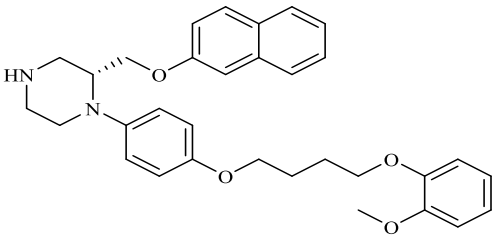
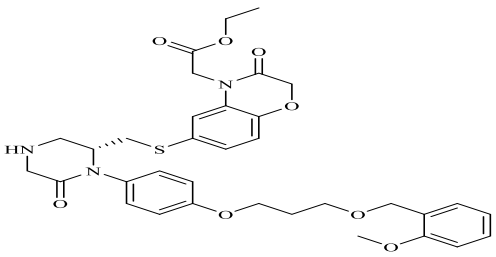
No.	Compound `s Structures	IC_{50}(µM) Experimental
45		42.000
46		1.000
47		76.375
48		20.933
49		33.857
50		0.597

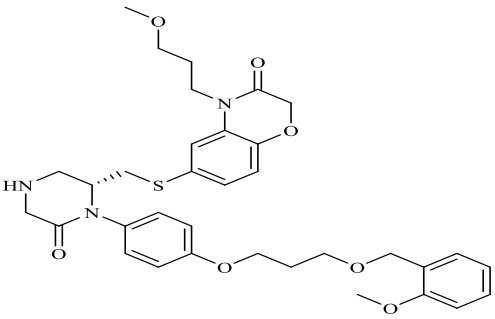
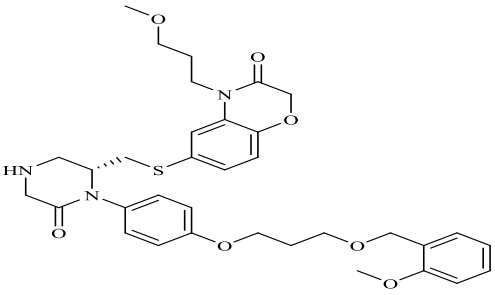
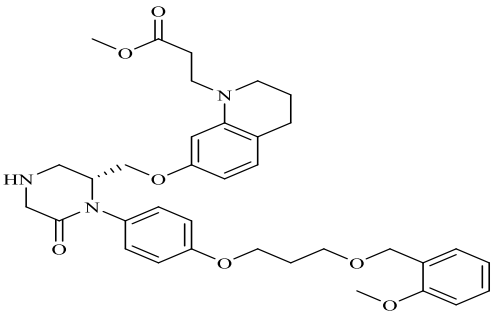
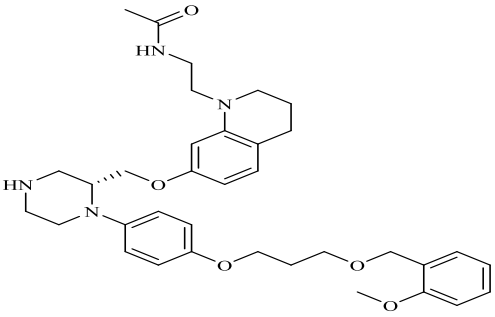
(Table 1) contd.....

No.	Compound `s Structures	IC_{50}(µM) Experimental
51		1.980
52		23.700
53		1.700
54		1.020
55		2.549
56		26.255

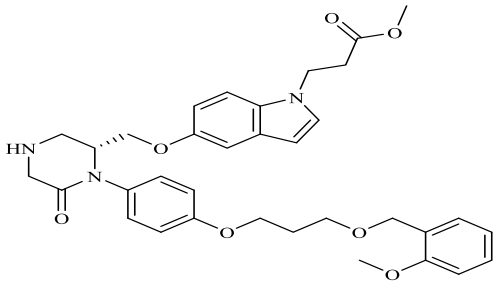
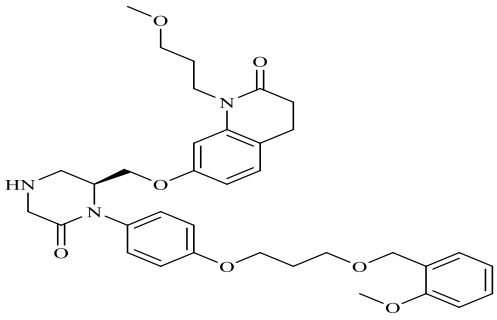
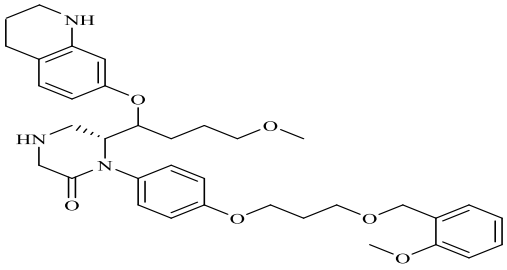
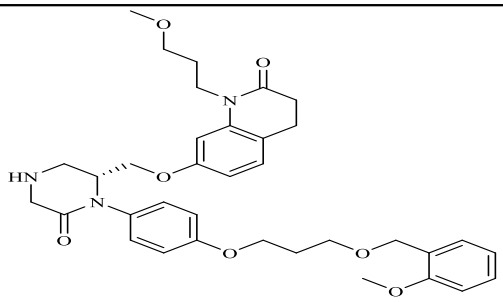
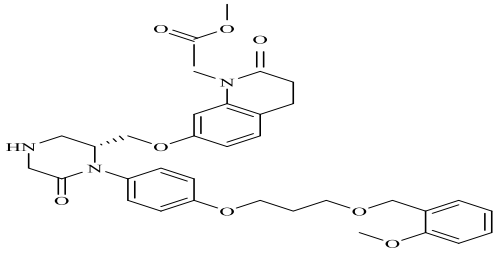
(Table 1) contd.....

No.	Compound `s Structures	IC_{50}(µM) Experimental
57		0.167
58		0.225
59		1.513
60		0.537
61		1.360
62		0.00017

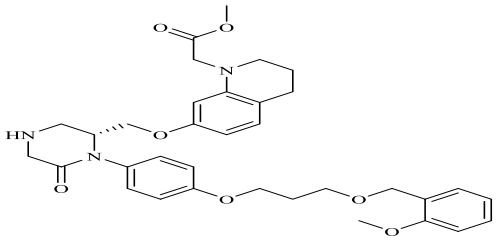
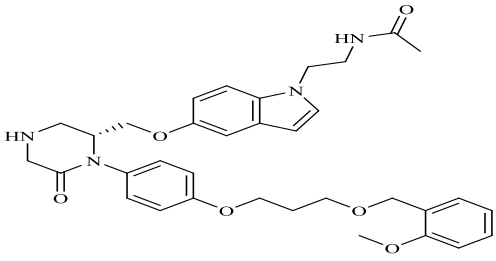
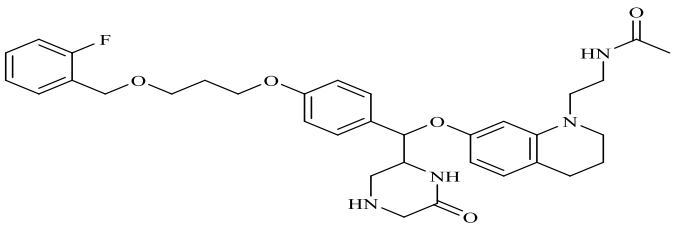
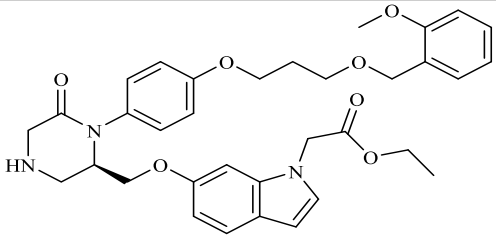
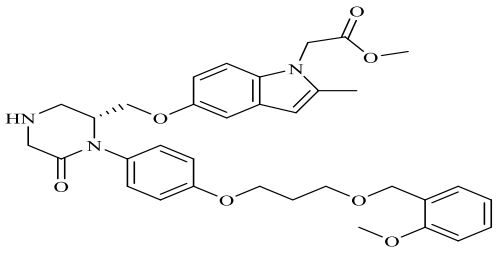
(Table 1) contd.....

No.	Compound `s Structures	IC_{50}(µM) Experimental
63		0.00018
64		0.00035
65		0.00036
66		0.00053

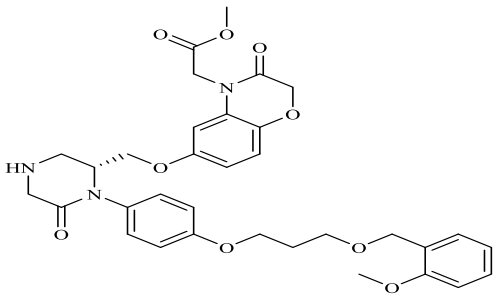
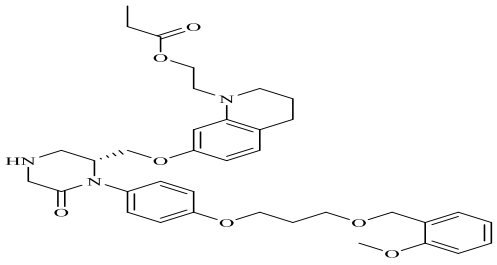
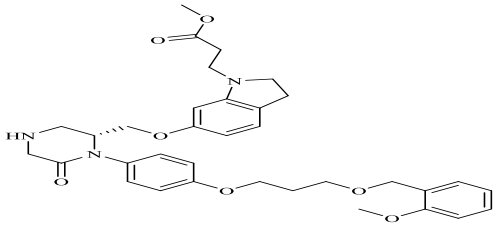
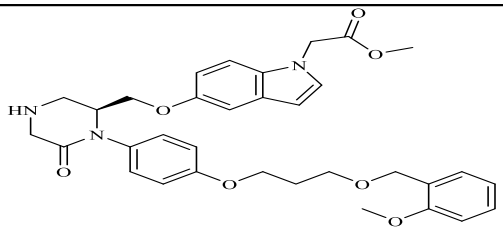
(Table 1) contd.....

No.	Compound `s Structures	IC_{50}(µM) Experimental
67		0.00162
68		0.00170
69		0.00317
70		0.00391
71		0.00400

(Table 1) contd.....

No.	Compound `s Structures	IC_{50}(µM) Experimental
72		0.00409
73		0.00466
74		0.00500
75		0.00600
76		0.00600

(Table 1) contd.....

No.	Compound `s Structures	IC_{50}(µM) Experimental
77		0.00683
78		0.00900
79		0.00959
80		0.01000

Molecules were randomly divided into the test set (24 molecules) and training set (56 molecules). The 2D structures were converted into 3D structures by using software Chem Office 2004, Version 8.0 [15]. The energy minimization was executed in two steps, in the first step energy minimized using molecular mechanics-2 (MM2) until the root mean square (RMS) gradient value attained the value smaller than 0.100 kcal/mol Å and then in second step minimized molecules were subjected to re-optimization by MOPAC (Molecular Orbital Package) module using the AM1 procedure foreclosed shell system until the RMS gradient reached a value smaller than 0.0001kcal/mol Å. Total 3224 molecular descriptors were calculated on the DRAGON Software, Version 5.5 (Table **2**) [16].

Table 2. calculate values of various descriptors intended for the compounds

NO.	[a]Sv	[b]nDB	[c]nO
1	46.11	1	5
2	44.51	1	5
3	43.22	1	5
4	43.33	1	5
5	43.81	1	5
6	43.81	1	5

(Table 2) contd.....

NO.	[a]Sv	[b]nDB	[c]nO
7	44.71	1	5
8	43.22	1	5
9	45.22	1	6
10	45.22	1	6
11	43.33	1	5
12	45.22	1	6
13	45.04	1	5
14	43.81	1	5
15	44.71	1	5
16	45.74	1	5
17	45.15	1	5
18	53.52	2	7
19	45.31	0	5
20	43.2	0	4
21	46.11	1	5
22	44.09	0	3
23	46.22	1	5
24	45.51	1	5
25	46.7	1	5
26	46.33	1	5
27	52.01	1	6
28	43.11	1	5
29	43.22	1	5
30	38.92	1	5
31	45.51	1	5
32	45.51	1	5
33	50.5	0	5
34	43.9	0	4
35	44.6	0	4
36	43.9	0	4
37	43.9	0	4
38	44.6	0	4
39	44.8	0	4
40	45.31	0	5
41	43.22	1	5
42	45.31	0	5
43	46.11	1	5
44	43.22	1	5
45	43.31	0	4
46	44.9	1	5
47	40.31	1	5
48	40.91	1	5
49	40.31	1	5
50	44.2	0	3
51	47.8	0	4
52	46.2	0	4
53	46.31	0	4
54	50.39	0	4
55	46.2	0	4
56	46.2	0	4
57	47.71	1	5
58	48.22	1	6
59	48.71	1	5
60	48.22	1	6

(Table 2) contd.....

NO.	[a]Sv	[b]nDB	[c]nO
61	46.2	0	4
62	52.92	3	8
63	53.01	2	7
64	53.01	2	7
65	53.52	2	7
66	54.09	1	5
67	51.32	2	7
68	53.52	2	7
69	53.61	1	6
70	53.52	2	7
71	51.84	3	8
72	51.92	2	7
73	51.81	2	6
74	52	2	5
75	51.32	2	7
76	51.32	2	7
77	50.75	3	9
78	55.12	2	7
79	51.92	2	7
80	49.73	2	7

[a]Sv sum of atomic van der Waals volumes (scaled on Carbon atom) Constitutional indices, [b]nDB number of double bonds Constitutional indices, [c]nO number of Oxygen atoms Constitutional indices.

Development of Quantitative structure–activity relationship model was carried out by sequential MLR method using VALSTAT program [17]. The validation of Quantitative structure–activity relationship models "Leave-one-out (LOO)" method was utilized. The greatest model was chosen on the basis of various statistical parameters such as correlation coefficient (R), square of correlation coefficient (R^2), sequential Fischer test (F). The correlative and predictive ability of the each model was estimated from the cross-validated squared correlation coefficient (Q^2), standard deviation of prediction (S_{PRESS}), and standard deviation of error of prediction (S_{DEP}). Bootstrapping square correlation coefficient (R^2_{bt}) was calculated which authenticate the robustness and applicability of QSAR equation. The derived QSAR model was applied for the prediction of the activity values of the compounds in the test set and the exterior validation parameter, predictive R^2 (R^2_{pred}) was calculated to assess the predictive capacity of the model. Various r_m^2 metrics were also calculated to validate the model further on stringent condition [18, 19].

The Z score method was adopted for the finding of outliers. Z score can be explaining as an 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 a Z score higher than 2.5, during generation of a particular QSAR model, is measured as an outlier.

RESULT AND DISCUSSION

In current study authors tried to develop a Quantitative structure–activity relationship model to clarify the correlation between physicochemical parameters and renin inhibitors. A data set of 80 piperazine and keto piperazine based renin inhibitors was used in the present study.

Several equations were raised when data set subjected to sequential multiple linear regression analysis. Out of these the most statistically significant equation was regarded as the best model.

BA= [-3.16542(± 2.41293)] + Sv [0.217772(± 0.0590015)] + nDB [1.19936(± 0.437316)] + nO [-0.322083(± 0.322204)]

The statistical parameters for this model are presented in Table **3**. The model presented above was considered as the best model due to its overall predictivity. The inter correlation between few descriptors was found to be high (Table **4**), which could be owing to synergistically interacting descriptors. Furthermore, the multicollinearity arising from utilization of correlated descriptors is not a serious problem as assumed often. There are several examples of cases where pairs of highly correlated, descriptors generated the highly significant regression equations [20 - 24].

Table 3. Quantitative structure–activity relationship statistics of important equation#.

Parameters	Statistical values
N Train	56
N test	24
NV	3
R	0.920
R^2	0.846
Variance	0.335
Std	0.578
F	95.465
R^2_{bt}	0.852
Chance	<0.001
Q^2	0.818
SPRESS	0.629
SDEP	0.606
R^2pred	0.821
r_m^2 (Loo)	0.799
r_m^2 (Predicated)	0.675
r_m^2(Overall)	0.782

#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. Correlation among structural descriptors and with the activity.

Parameters	$logIC_{50}$(M)	Sv	nDB	nO
$logIC_{50}$(M)	1			
Sv	0.838511	1		
nDB	0.786293	0.594754	1	
nO	0.751425	0.673352	0.911668	1

The model displays a good (R) of 0.920 between the descriptors Sv, nDB, nO for rennin binding affinity. The squared (R^2) of 0.846 indicates 84.6 % of the variance in the biological activity. This model also illustrates significance level more than 95% with F value =95.465, a low standard deviation of estimation 0.578, establish the accuracy of the model. The stability of the model evaluated by leave-one-out method is literally superior ($Q^2 > 0.6$) suggesting the effectiveness of model for consequential predictions. The robustness of model was shown by magnitude of the R^2_{bt} (0.852), which was close to conventional $R^2$0.846). Additional help in this regard was found from the small values of the cross-validation parameters S_{PRESS} and S_{DEP}. The predicted R^2 value of the test sets was 0.821, representing brilliant predictive capacity of the model. The calculated, predicted and observed values of biological activity are exposed in Table **5** and Table **6** respectively. The association between predicted activity (LOO) and observed of the training and test set is shown in Fig. (**1**).

Table 5. Comparative biological activity [$logIC_{50}$ (M)] of the training set.

Compound no.	Observed activity	Calculated activity	Predicted activity
1	7.180	6.465	6.446
2	6.742	6.117	6.095
3	6.648	5.836	5.793
4	6.609	5.860	5.821
6	6.488	5.964	5.941
7	6.472	6.160	6.150
9	6.213	5.949	5.928
10	6.056	5.949	5.941

(Table 5) contd.....

Compound no.	Observed activity	Calculated activity	Predicted activity
11	5.803	5.860	5.863
13	7.167	6.232	6.203
14	6.652	5.964	5.934
16	6.971	6.384	6.369
17	6.879	6.256	6.237
19	5.399	5.091	5.053
20	4.963	4.954	4.954
22	5.848	5.470	5.421
25	6.907	6.594	6.585
27	7.432	7.428	7.427
28	5.154	5.812	5.848
29	5.253	5.836	5.867
32	5.462	6.334	6.359
33	7.194	6.222	6.054
34	4.360	5.106	5.139
36	5.298	5.106	5.098
37	4.799	5.106	5.120
38	5.363	5.259	5.254
40	4.807	5.091	5.127
41	5.416	5.836	5.858
42	4.516	5.091	5.163
43	5.762	6.465	6.484
44	5.388	5.836	5.859
45	4.377	4.978	5.006
49	4.470	5.202	5.301
50	6.224	5.494	5.398
52	4.625	5.607	5.660
53	5.770	5.631	5.624
54	5.991	6.520	6.604
55	5.594	5.607	5.608
56	4.581	5.607	5.662
60	6.270	6.602	6.618
61	5.866	5.607	5.594
62	9.770	9.381	9.329
65	9.444	8.634	8.571
67	8.790	8.155	8.121
68	8.770	8.634	8.623
69	8.499	7.776	7.685
70	8.408	8.634	8.651
71	8.398	9.145	9.246
73	8.332	8.584	8.613
74	8.301	8.947	9.247
75	8.222	8.155	8.151
76	8.222	8.155	8.151
77	8.166	8.586	8.703
78	8.046	8.982	9.090
79	8.018	8.285	8.301
80	8.000	7.809	7.798

Table 6. Comparative biological activity [logIC_{50} (M)] of the test set.

Compound no.	Observed activity	Predicted activity
5	6.530	5.964
8	6.343	5.836

(Table 6) contd.....

Compound no.	Observed activity	Predicted activity
12	5.413	5.949
15	6.429	6.160
18	9.377	8.634
21	7.268	6.465
23	6.818	6.489
24	6.085	6.334
26	6.054	6.513
30	5.416	4.899
31	6.277	6.334
35	4.939	5.259
39	4.220	5.302
46	6.000	6.202
47	4.117	5.202
48	4.679	5.333
51	5.703	5.956
57	6.777	6.813
58	6.648	6.602
59	5.820	7.031
63	9.745	8.523
64	9.456	8.523
66	9.276	8.203
72	8.388	8.285

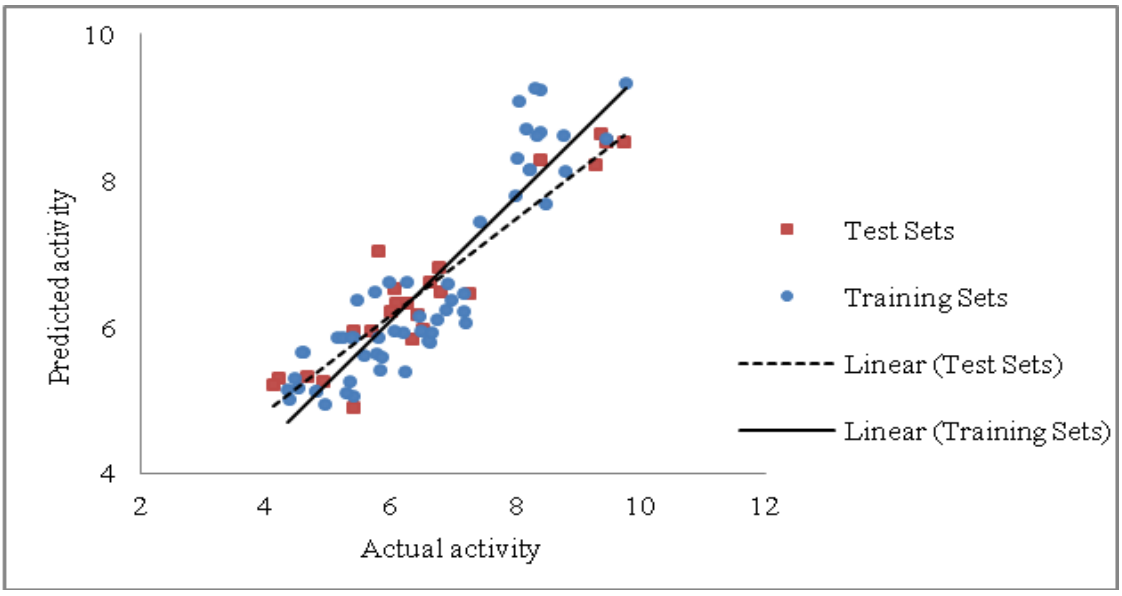


Fig. (1). Chart of actual activity *vs*. predicted activity for the training set and test set.

The QSAR study revealed that Sv and nDB descriptors have positive involvement to the renin inhibitory activity while nO has negative contribution to the renin inhibitory activity. All the three descriptors are 0D-constitutional indices, which are independent from molecular connectivity and conformations [25]. The predominant positive effect of Sv can be seen by observing the most potent compounds (compound no. 18 and 62-65). All these compounds have benzo-oxazine moiety with ester or ether side chain or tetrahydro quinoline with amide side chain, which provide bulkiness to molecule as shown in Fig. (**2**).

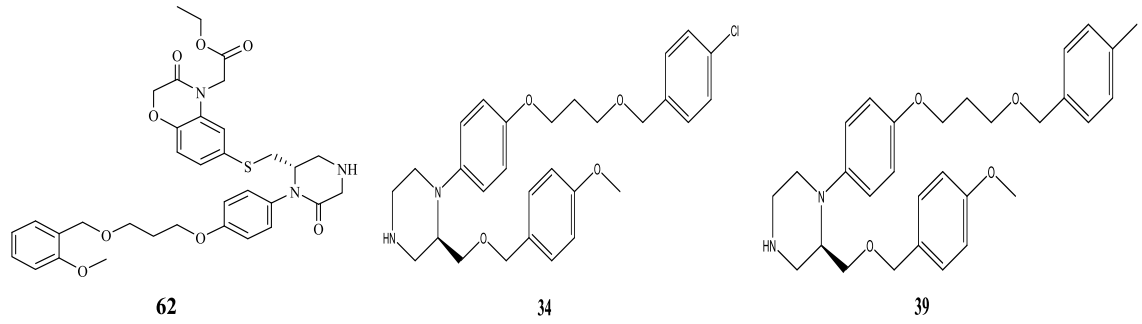
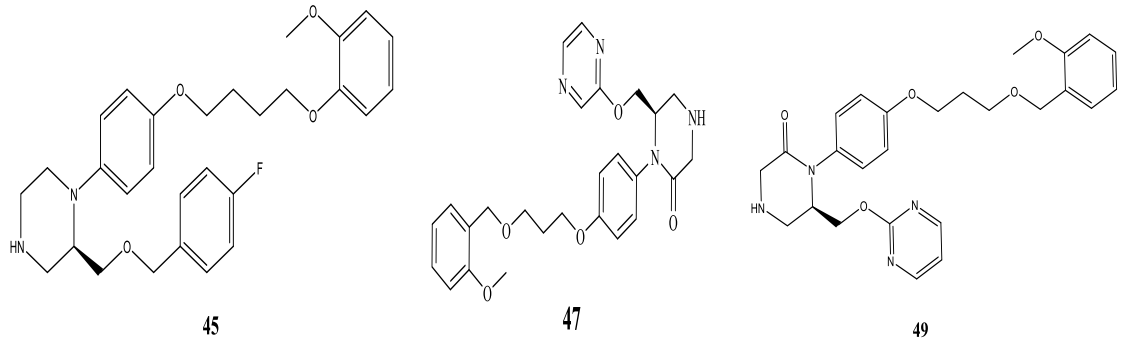


Fig. (2). Structures of most potent compound (62) and least potent compound (34, 39, 45, 47, and 49).

There are hydrophobic and hydrophilic amino acids both in the renin molecule. The hydrophilic amino acids are found outside the molecule, while the hydrophobic amino acids tends to be more on the inner side. The hydrophobic amino acids form the active site, a large hydrophobic pocket which can cover a molecule with minimum seven residues. Hydrogen bonding is the prime link between a renin and the ligand [26, 27]. For efficient and specific binding, the receptor cavity, in most cases, must be tightly filled with the interacting ligand. The increased van der Waals volumes could be helping the drug to place the drug residue in close proximate with amino acids in the hydrophobic pocket. The least potent compounds (compound no. 34, 39, 47, 49) are free from bulkiness provided by benzo-oxazine moiety or quinoline rings in Fig. (**2**). Positive contribution of nDB indicates that introduction of extra aromatic/heterocyclic ring or doubly bonded hetero atom increases the binding affinity. It is clearly seen that all the most potent compounds have extra one or two carbonyl group either as an ester or an amide. The little negative effect of descriptor nO is due to replacement of ether linkage between piperazine and benzoxazine ring, with thioether in most potent compounds (compound no. 62 and 63).



CONCLUSION

A developed QSAR model for piperazines and keto piperazines was found to be robust and accurate. This model can be used for designing the novel renin enzyme inhibitors in future.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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