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Prediction of Antihypertensive Activity of Substituted Piperidines as Highly Potent Renin Inhibitors Due to induced Fit Adaptation of the Active Fit Site

Shailja Sachan[1]*, Amitabh Tripathi[2], Pradeep Chandra Shukla[3]

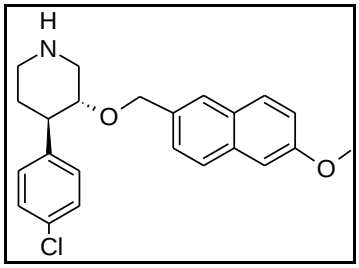
[1]Department of Chemistry, Govt. MSG College,Rewa, M.P. India,
[2]Department Of Chemistry, Awadhesh Pratap Singh University, Rewa, M.P. India,
[3]Department Of Chemistry, Y.P.S. College, Sirmour, Rewa, M.P., India

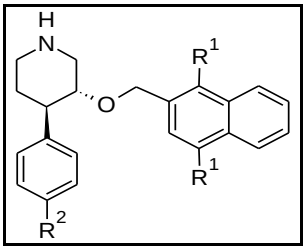
Abstract : We have studied a series of substituted Piperidines for predicting their Antihypertensive Activity of Renin inhibition on QSAR models.We have chosen certain descriptors viz. ZM1, Pol, MSD, CSI, X0, J_A,Wi_D, Wi_H2 and Hy in our study and found that molecular descriptors Hydrophilic factor, Eccentric Connectivity index, zero order connectivity index and Wiener-like index from topological distance matrix are very closely related with antihypertensive activity of these compounds.

Keywords: Antihypertensive, Piperidines, Renin Inhibitors, QSAR Study.

Introduction:

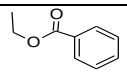
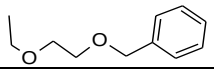
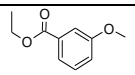
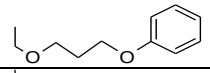
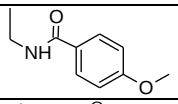
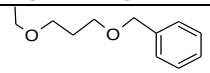
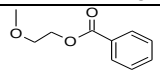
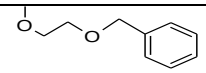
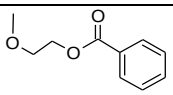
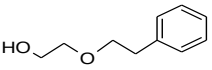
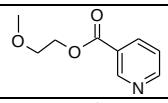
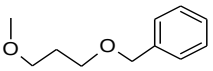
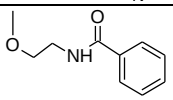
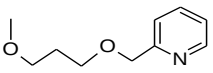
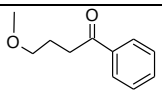
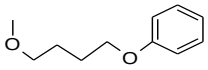
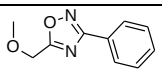
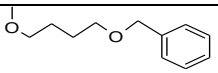
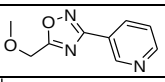
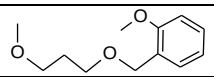
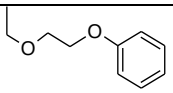
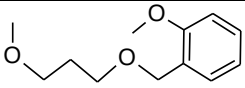
We have referred to the paper of Eric Vieraet al[1] in which they have observed that the renin-angiotensin system (RAS) is widely accepted as a major regulator of cardiovascular and renal function.[2,3]Itconsists of two-step cascade which generate the biologically active angiotensin (Ang) II from angiotensinogen by the aspartic proteinase renin, followed by angiotensin-converting enzyme (ACE). Renin inhibition results in a total blockage specific. Thus, renin inhibition produces an antihypertensive effect comparable to that seen with ACE inhibitors and angiotensin II receptor antagonists,[4-6] but free of side effects due to insufficient specificity. The expected improved efficacy in the tissular system of heart,[7,8] and kidney[9-11]gives renin inhibitors the potential for improved prevention and the treatment of end organ damage.[12]Eric et al after screening the Roche Compound Library had identified a compound trans-4-(4-chlorophenyl)-3-(4-methoxybenzyl)-piperidine, **rac-2** which exhibited weak inhibition of human renin (IC_{50}= 50 µM) devoid of any inhibitory activity against HIV protease, porcine pepsin or bovine cathepsin D. We have taken a set of compounds identified by them along with their renin inhibiting activity in Table 1 for our study. These compounds have been derived from the structure given in Fig 1.





rac-2 **Fig 1**

Table 1 - List of Compounds and Ic_{50} Values:

Compound	R1	R2	IC_{50} [µM]	Compound	R1	R2	IC_{50} [µM]
rac-23	H		55	rac-34	H		91
rac-24	H		87	rac-35	H		$5.4x10^2$
rac-25	H		$>10^5$	rac-36	H		$7.4x10^2$
rac-26	H		$4.0x10^4$	rac-37	H		53
rac-27	H		26	rac-38	H		$1.6x10^2$
rac-28	H		$5.8x10^2$	rac-39	H		8.0
rac-29	H		$2.6x10^3$	rac-40	H		$2.1x10^2$
rac-30	H		$2.2x10^2$	rac-41	H		$2.2x10^2$
rac-31	H		41	rac-42	H		$1.0x10^2$
rac-32	H		$8.8x10^2$	rac-43	H		1.5
rac-33	H		$1.6x10^2$	rac-44			0.060

Methods And Material:

Now we used Dragon 6[©13]software (Molecular descriptor Calculation software) to calculate various molecular and structural descriptors out of which we have chosen some descriptors, which appeared to be closely related with renin inhibiting activity of these compounds. Since the value of IC_{50} was varying in a large range, we have taken its logarithmic value. IC_{50} is the quantity of these

compounds in micromoles (µM) which is experimentally required to inhibit the activity of human renin by 50%. Table-2 gives logarithmic values of IC_{50} and value of different descriptor for the given set of compounds as calculated by Dragon6. These descriptors are ZM1[14], Pol[15], MSD[16], CSI[17], X0[18], J_A[19],Wi_D[20], Wi_H2[21] and Hy[22]. Details of these descriptors are given in Table-3

Table 2- Calculated Value of Descriptors:

Comps.	Log IC_{50}	ZM1	Pol	MSD	CSI	X0	J_A	Wi_D	Wi_H2	Hy
rac-23	1.740362689	178	52	8.815	1150	23.167	106.1413	4197	65.09	-0.48
rac-24	1.939519253	188	56	9.285	1274	24.744	117.94	4958	69.109	-0.465
rac-25	5	188	56	9.413	1322	24.744	117.94	5014	68.973	0.066
rac-26	4.602059991	186	55	8.866	1183	24.089	111.0359	4482	67.693	0.105
rac-27	1.414973348	186	54	9.721	1338	24.581	118.3944	5166	68.3	-0.465
rac-28	2.763427994	186	54	9.721	1338	24.581	118.3944	5166	68.3	-0.438
rac-29	3.414973348	186	54	9.721	1338	24.581	118.3944	5166	68.3	0.066
rac-30	2.342422681	186	54	9.721	1338	24.581	118.3944	5166	68.3	-0.493
rac-31	1.612783857	198	56	9.66	1405	24.865	109.8888	5433	72.126	-0.445
rac-32	2.944482672	198	56	9.66	1405	24.865	109.8888	5433	72.126	-0.419
rac-33	2.204119983	180	51	9.631	1301	23.711	112.765	4826	65.99	-0.486

rac-34	1.959041392	184	52	10.08	1400	24.418	118.9898	5334	67.619	-0.493
rac-35	2.73239376	184	52	10.08	1400	24.418	118.9898	5334	67.619	-0.493
rac-36	2.86923172	188	53	10.533	1501	25.125	125.3812	5878	69.248	-0.499
rac-37	1.72427587	180	51	9.631	1301	23.711	112.765	4826	65.99	-0.486
rac-38	2.204119983	184	52	10.08	1400	24.418	118.9898	5334	67.619	-0.493
rac-39	0.903089987	184	52	10.08	1400	24.418	118.9898	5334	67.619	-0.493
rac-40	2.322219295	184	52	10.08	1400	24.418	118.9898	5334	67.619	-0.465
rac-41	2.342422681	184	52	10.08	1400	24.418	118.9898	5334	67.619	-0.493
rac-42	2	188	53	10.533	1501	25.125	125.3812	5878	69.248	-0.499
rac-43	0.176091259	194	57	10.524	1488	25.995	131.5801	6219	71.72	-0.479
rac-44	-1.22184875	214	68	10.777	1652	29.15	158.7872	7813	80.964	-0.455

Table 3- Details of descriptors Used:

Sn.	Descriptors	Descriptors Detailed name
1	**ZM1**	The first Zagreb index (ZM1) is the sum of the squared vertex degrees of all the non-hydrogen atoms.
2	**Pol**	The polarity number (Pol) is calculated as the number of pairs of vertices at a topological distance equal to three.
3	**MSD**	The mean square distance index (MSD) is calculated as follows: $$MSD = \sqrt{\frac{\sum_{i=1}^{nSK}\sum_{j=1}^{nSK} d_{ij}^2}{nSK \cdot (nSK-1)}}$$ wheredij is the topological distance between two atoms and nSK is the number of non-hydrogen atoms
4	**CSI**	The eccentric connectivity index (CSI) is calculated as the sum over all non-hydrogen atoms of the product of atom eccentricity (i.e., the maximum topological distance from an atom to any other atoms) and vertex degree.
5	**X0**	Kier-Hall molecular connectivity indices (X*k*, *k* being the order) are derived from the simple vertex degrees.
6	**J_A**	The adjacency matrix (A) is a square binary matrix, whose elements equal 1 if they correspond to pairs of adjacent atoms. The Wiener-like index of this matrix coincides with the number of non-H bonds (nBO) and the Randic-like index with Kier-Hall connectivity index of order 1 (X1).
7	**Wi_D**	The Wiener index (Wi_D) is calculated as the half-sum of all topological distances collected in the distance matrix.
8	**Wi_H2**	The reciprocal squared distance matrix (H2) collects reciprocal squared topological distances between any pair of non-H atoms. The Wiener-like index of this matrix (Wi_H2) is calculated as the sum of all the reciprocal squared topological distances in a H-depleted molecular graph and is commonly known as Harary number.
9	**Hy**	The hydrophilic factor (Hy) is a hydrophilicity descriptor defined as $$Hy = \frac{(1+N_{Hy})\cdot\log_2(1+N_{Hy}) + nC\cdot\left(\frac{1}{nSK}\cdot\log_2\frac{1}{nSK}\right) + \sqrt{\frac{N_{Hy}}{nSK^2}}}{\log_2(1+nSK)}$$ whereN_{Hy} is the number of hydrophilic groups (-OH, -SH, -NH), nC the number of carbon atoms and nSK the number of atoms (hydrogen excluded).

We know that QSAR analysis is one of the most effective approaches for optimizing lead compounds and designing new drugs. Excellent QSAR model can aid in understanding the mechanism of the action of drugs and may save the cost and time in the course of developing a new drug when compared with empirical procedures.[23-25] Hence, after calculating various descriptors we applied QSAR techniques to visualize any relationship among the descriptors and the activity. We have used NCSS 2007[26] for statistical analysis of the data in hand.The relatedness among the descriptors used and their correlation with rennin inhibiting

antihypertensiveactivity(IC_{50}) is demonstrated in Table4. This shows that almost all variables have statistically significant correlation with antihypertensive activity. Results of regression analysis are given in the Table5. The result of cross validation analysis is given in the Table-6, Finally Table-7 shows the predicted and observed antihypertensive activity with residuals.

Table 4-Corelation Matrix of Descriptors:

	Log IC_{50}	**ZM1**	**Pol**	**MSD**	**CSI**	**X0**	**J_A**	**Wi_D**	**Wi_H 2**	**H y**
Log IC_{50}	1									
ZM1	-0.45071	1								
Pol	-0.43567	0.92524	1							
MSD	-0.53651	0.435801	0.276986	1						
CSI	-0.54799	0.686013	0.516199	0.947433	1					
X0	-0.56916	0.907122	0.911085	0.645141	0.807035	1				
J_A	-0.60545	0.695995	0.756786	0.747139	0.807832	0.932771	1			
Wi_D	-0.6352	0.825724	0.749125	0.840469	0.9436	0.950858	0.928673	1		
Wi_H2	-0.51605	0.98992	0.944143	0.500905	0.730594	0.954276	0.7857	0.879888	1	
Hy	0.665909	0.006326	0.142819	-0.44618	-0.35753	-0.06895	-0.14783	-0.25574	-0.03223	1

Table 5-Results of regression Analysis:

Model No.	**Parameters Used**	**Ai (1-7)**	**Intercept**	**MSE**	**R^2**	**AR^2**	**F-Ratio**	**Q= R/MSe**
1	**Hy**	4.4324±1.1104	3.9547	0.99594	0.4434	0.4156	15.935	0.6686
2	**Wi_D**	-0.0012±0.0003	8.4729	1.06744	0.4035	0.3737	13.528	0.5951
3	**Hy** **Pol**	4.9475±0.8002 -0.1975±0.0438	14.8635	0.50664	0.7310	0.7027	25.819	1.6876
4	**X0** **Hy**	-0.6043±0.1402 4.1911±0.8121	18.8044	0.53018	0.7185	0.6889	24.252	1.5988
5	**J_A** **Hy**	-0.0647±0.0157 3.9223±0.8368	11.4794	0.55334	0.7062	0.6753	22.839	1.5187
6	**Hy** **CSI** **Wi_D**	4.5770±0.7567 0.0145±0.0040 -0.0029±0.0006	-0.1907	0.37533	0.8112	0.7798	25.784	2.3997
7	**Hy** **CSI** **X0**	4.9875±0.8999 0.0048±0.0028 -0.9607±0.2458	21.3692	0.48008	0.7585	0.7183	18.849	1.8141
8	**Wi_H2** **Hy** **ZM1**	-0.9611±0.3461 3.8428±0.8065 0.3207±0.1445	9.8269	0.48660	0.7553	0.7145	18.516	1.7860
9	**Hy** **Pol** **J_A**	4.5349±0.8607 -0.1288±0.0713 -0.0296±0.0244	14.5145	0.49444	0.7513	0.7099	18.127	1.7530
10	**Hy** **CSI** **X0** **Wi_D**	3.5184±0.8646 0.0288±0.0079 1.8872±0.9139 -0.0080±0.0025	-40.0632	0.31772	0.8491	0.8136	23.910	2.7281
11	**Hy** **Pol** **CSI** **Wi_D**	4.0875±0.8301 0.1645±0.1251 0.0231±0.0076 -0.0048±0.0016	-10.9296	0.36073	0.8286	0.7883	20.552	2.5234

	Hy **MSD** **CSI** **Wi_D**	4.3529±0.7840 -1.0455±0.9941 0.0210±0.0073 -0.0033±0.0007	2.8397	0.37313	0.8228	0.7811	19.729	2.4310
12*	**Hy** **CSI** **X0** **Wi_D**	3.5031±0.7516 0.0291±0.0068 1.7702±0.7958 -0.0078±0.0022	-38.2394	0.24008 9	0.8873	0.8591	31.484	3.9234

1-logIC50 = 14.8635+4.9475±0.8002 Hy-0.1975±0.0438 Pol
n=22, MSE=0.5066, R2=0.7310, AR2=0.7027, F-Ratio = 25.819, Q= 1.6876

2 - logIC50 =-0.1907+4.5770±0.7567Hy+0.0145±0.0040CSI-0.0029±0.0006Wi_D
n=22, MSE=0.3753, R2=0.8112, AR2=0.7798, F-Ratio = 25.784, Q= 2.3997

3- logIC50 =-40.06323+5184±0.8646Hy+0.0288±0.0079CSI+1.8872±0.9139X0-0.0080±0.0025 Wi_D
n=22, MSE=0.3177, R2=0.8491, AR2=0.8136, F-Ratio = 23.910, Q= 2.7281

4- logIC50 =-38.2394+3.5031± 0.7516Hy+0.0291±0.0068 CSI+1.7702±0.7958 X0-0.0078±0.0022Wi_D
n=22, MSE=0.2401, R2=0.8873, AR2=0.8591, F-Ratio = 31.484, Q= 3.9234

Table 6- Results of cross Validation:

Model No.	**PRESS**	**SSY**	**PRESS/SSY**	**R^2_{CV}**	**SPRESS**
3	16.5073	35.7888	0.4612	0.5388	0.9321
6	9.9731	35.7888	0.2787	0.7213	0.7444
10	8.7639	35.7888	0.2449	0.7551	0.7180
12[%]	7.7743	35.7888	0.2172	0.7718	0.6971

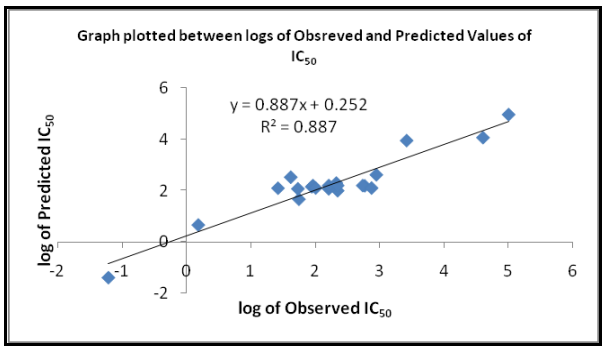
[%]**This model was calculated after deleting compound rac-39 to improve the results**.

PRESS→ Predicted Residual Sum of Squares, **SSY→** Sum of Squares of Y, **R^2_{CV}→** Cross Validative Coefficient of determination, **SPRESS→** Uncertainty of prediction

Table 7- Predicted and Observed Antihypertensive Activity Along with Residuals for Model 12 of Table 6:

Compounds	**Observed log IC_{50}**	**Predicted log IC_{50}**	**Residual**
rac-23	1.74	1.671	0.069
rac-24	1.94	2.158	-0.219
rac-25	5	4.978	0.022
rac-26	4.602	4.078	0.524
rac-27	1.415	2.103	-0.688
rac-28	2.763	2.197	0.566
rac-29	3.415	3.963	-0.548
rac-30	2.342	2.005	0.338
rac-31	1.613	2.533	-0.92
rac-32	2.944	2.624	0.32
rac-33	2.204	2.078	0.126
rac-34	1.959	2.205	-0.246
rac-35	2.732	2.205	0.528
rac-36	2.869	2.11	0.759
rac-37	1.724	2.078	-0.354
rac-38	2.204	2.205	-0.001
rac-40	2.322	2.303	0.019
rac-41	2.342	2.205	0.138
rac-42	2	2.11	-0.11
rac-43	0.176	0.667	-0.491
rac-44	-1.222	-1.391	0.169

GRAPH:



Result and Discussion:

Correlation matrix shows that antihypertensive activity is correlated with certain descriptors by a ratio of more than 0.6000. These descriptors are J_A, Wi_D are Hy. X0 and CSI are also significantly related. All the descriptors are correlated negatively except **Hy** which is positive. Interrelation is highest between ZM1 and Wi_H2 i.e. 0.9899 and both of these are not part of our best models. Regression analysis of different parameters with respect to antihypertensive activity shows that in mono parametric regression only two parameters Hy and Wi_D have given a value of 0.4434 and 0.4035 respectively for R2 and they can be taken as satisfactory as they are part of our best models in multiple regressions. Our next best model is tri-parametric with parameters Hy, CSI and Wi_D which is giving an R^2 of 0.8112 thus proving close relation of these parameters with the activity. Since number of compounds taken for present study is 21, we have carried out multiple regression upto four parameters. The best tetra-parametric model is giving an R^2 of 0.8873 which showing a better dependence of the activity on parameters viz**Hy, CSI, X0, Wi_D.** Earlier we had eliminated compound rac-39 as an outliner in order to improve our result. This elimination also eliminated parameter **Pol** from our best model which had also not appeared in our other best models but was getting in the way due to that compound. thus elimination was justified.

Cross validation has given PRESS/SSy value as 0.2172 for our best model which is well within limits. The quality factor Q is also highest for our best model (12). R^2_{CV} is also very close to regular R^2wich shows validity of our results.

Conclusion:

From the set of compounds we have studied, we conclude that molecular descriptors Hydrophilic factor, Eccentric Connectivity index, zero order connectivity index and Wiener-like index from topological distance matrix are very closely related with antihypertensive activity of these compounds. Contribution of all except Wi_D is positive.

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26. NCSS 329 North 1000 EastKaysville, Utah 84037Phone (801) 546-0445 Fax (801) 546-3907 Email: support@ncss.com

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