International Journal of Drug Design and Discovery

Volume 2 ● *Issue* 1 ● *January – March* 2011. 375-382

QSAR Modeling of Substituted Benzimidazole Derivative as Angiotensin II-AT_1 Receptor Antagonist: WHIM Descriptors

Vivek K.Vyas* and Manjunath Ghate

Department of Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University, Ahmedabad, 382 481 Gujarat, India.

ABSTRACT: Selective inhibition of Angiotensin II (Ang II) is an important strategy for design of Ang II-AT_1 receptor antagonist which is devoid of the common side effects of angiotensin converting enzyme inhibitors (ACEIs). QSAR study of 4, 5, 6, and 7 substituted benzimidazole analogs were performed using Dragon 2.1 (Milano Chemometrics) for antagonism of Ang II. The study was carried out on 33 compounds; mathematical models were obtained by means of the sequential multiple linear regression analysis (SMLR). QSAR analysis have produced good predictive models and give statistically significant correlations of selective Ang II antagonism with WHIM descriptors concerning size, symmetry, shape and distribution of molecules atom. The predictive ability of the resulting QSAR model was evaluated by cross validated correlation coefficient (q^2 = 0.659). It was able to describe more than 68% of the variance in the experimental activity. This QSAR study helps in design and prediction of Ang II inhibitory activity of novel substituted benzimidazole Ang II-AT_1 receptor antagonist.

KEYWORDS: QSAR; Ang II antagonist; AT_1 and AT_2 receptors; Substituted benzimidazole derivatives; Weighted holistic invariant molecular (WHIM) descriptors

Introduction

The renin –angiotensin system (RAS) is known to play an important role in the regulation of fluid, electrolyte balance and blood pressure[1]. The linear octapeptide Angiotensin II (Ang II) is a potent vasoconstrictor produced by the RAS cascade which regulates blood pressure homeostasis, fluid volume and electrolyte balance. The Ang II interacts with AT_1 receptor causing aldosterone secretion, renal sodium retention, vasoconstriction and other biological effects[2-4]. Interaction of Ang II with AT_1 receptor is mainly responsible for virtually all of the well-known physiological actions of Ang II in cardiovascular, neuronal, renal, hepatic, endocrine and other target cells[5]. Inhibition of the RAS is an effective way to control pathogenesis of cardiovascular and renal disorders. Renin inhibitors and angiotensin converting enzyme inhibitors (ACEIs) were the earliest of the RAS blocking agents to have broad therapeutic success in the treatment of congestive heart failure, renovascular hypertension and essential hypertension[6-8]. Antagonism of Ang II constitutes an alternative method for blocking the RAS. Several peptidic and nonpeptidic Ang II receptor antagonists are known; both the antagonists block the action of Ang II on AT_1 binding site in a competitive and reversible manner but can display non-classical patterns of antagonism[9]. Ang II receptor blockers (ARBs) act by inhibiting Ang II actions at the receptor level, rather than by inhibiting its synthesis. The therapeutic profile of Ang II receptor antagonist is thought to be similar to that of ACEIs such as captopril, enalapril and lisinopril. In addition, since ARBs does not affect the metabolism of bradykinin; they may not have the side effect of ACEIs, such as dry cough. Losartan[10] is a selective AT_1 antagonist and the first agent of this class of drugs. The available data from the literature has explain the extensive SAR work based upon replacement of imidazole (losartan) with other heterocyclic (benzimidazole) ring, for this purpose different substitutions in benzimidazole nucleus have been studied, among them candesartan[11] and telmisartan[12] are found to be favorable Ang II-AT_1 receptor antagonist. To gain insight into the structural and molecular requirement influencing the Ang II antagonistic activity, we herein describe QSAR analysis of 2- butyl-4, 5, 6 and 7 substituted benzimidazole derivatives as Ang II antagonist.

* *For correspondence:* Vivek K. Vyas,

Tel.: +91 9624931060 Fax: +91 2717 241916

E-mail: vicky_1744@yahoo.com,

vivekvyas@nirmauni.ac.in (V.K.Vyas)

Material and Method

Data preparation

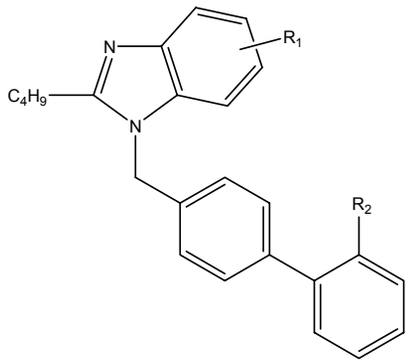
The Ang II-AT_1 receptor antagonistic activity data of substituted benzimidazole derivatives were collected from the literature[13]. The experimental IC_{50} values were evaluated by Keiji Kubo *et al.*[13] by inhibition of specific

binding of [^{125}I] Ang II (0.2 nM) to bovine adrenal cortex (inhibit 50% of bound [^{125}I] Ang II). The IC_{50} value data were converted to negative logarithmic value (concentration expressed in mole per liter) and subsequently used as the response variable for QSAR analysis and it is listed in Table 1.

Model building

All the calculation to draw out molecular descriptor was done on P-IV processor using CS Chem office version 8.0[14] and DRAGON[15], in order to perform correlation analysis VALSTAT[16] software was used. Before calculating the molecular descriptors, we carried out geometry optimization calculations for each compound of this study using the quantum chemical semiempirical method. The structure of substituted benzimidazole derivatives were drawn in Chem draw 8.0 and was copied to Chem 3D ultra 8.0 to create 3D model, which was served as template model. For every compound the template compound was suitably modified considering its structural feature so that every compound maintains same sequence of atoms. Minimized molecules are than subjected to re-optimization via Austin model-1 (AM1) method using closed shell restricted wave function of MOPAC module until the root mean square (RMS) gradient attained a value less than 0.0001 kcal/mol Å. The geometry optimization of the lowest energy structure was carried out using EF routine. The molecule was saved as MOL file format. Pursuly, the MOL file was used for calculation of various physicochemical properties using Dragon 2.1 ((Milano Chemometrics). Four kinds of molecular descriptors (Table 1) including different groups: WHIM, empirical, functional group and geometrical descriptors were calculated for this set of compounds with constant or near constant values inside each group of descriptors were discarded.

Table 1 Structure, activities and molecular properties of 2-butyl 4,5,6 and 7 substituted benzimidazole used in QSAR



Comp. No.	R_1	R_2	IC_{50}[a]	pIC_{50}[b]	nHAcc	E3s	G1s	Vs	E3u	Ap
1	H	Tetrazole	9.0	6.045	6	0.343	0.168	208.533	0.375	110.035
2	5-OMe	Tetrazole	9.1	6.041	7	0.347	0.165	279.878	0.397	135.953
3	6- OMe	Tetrazole	11	5.958	7	0.37	0.165	302.637	0.385	146.309
4	5-Cl	Tetrazole	15	5.823	6	0.345	0.167	308.894	0.355	131.411
5	6-Cl	Tetrazole	31	5.508	6	0.414	0.167	263.739	0.38	122.796
6	7- OMe	Tetrazole	28	5.552	7	0.312	0.163	269.718	0.314	119.61
7	4-CO_2Me	Tetrazole	72	5.142	8	0.243	0.163	269.718	0.314	119.61
8	5-CO_2Me	Tetrazole	7.4	6.131	8	0.334	0.163	404.567	0.376	154.089
9	6-CO_2Me	Tetrazole	4.4	6.356	8	0.335	0.163	390.607	0.349	174.082
10	7-CO_2Me	Tetrazole	3.2	6.498	8	0.335	0.163	334.662	0.418	145.933
11	5-Me,7-CO_2Me	Tetrazole	8.7	6.061	8	0.304	0.162	372.682	0.427	165.464
12	5-Cl, 7-CO_2Me	Tetrazole	4.4	6.356	8	0.308	0.162	390.278	0.411	155.269
13	6-Me,7-CO_2Et	Tetrazole	9.1	6.041	8	0.324	0.161	338.082	0.375	162.238

Table 1 *Contd…*

Comp. No.	R_1	R_2	IC_{50}[a]	pIC_{50}[b]	nHAcc	E3s	G1s	Vs	E3u	Ap
14	4-$CONH_2$	Tetrazole	130	4.886	8	0.241	0.164	231.635	0.415	124.196
15	7-CO_2Et	Tetrazole	14	5.856	8	0.314	0.162	369.066	0.318	160.798
16	7-COOBu	Tetrazole	13	5.886	8	0.581	0.167	459.741	0.306	181.69
17	5-COOH	Tetrazole	55	5.251	8	0.348	0.164	361.524	0.371	137.22
18	6-COOH	Tetrazole	90	5.045	8	0.353	0.164	392.131	0.365	149.113
19	7-COOH	Tetrazole	5.5	6.259	8	0.412	0.164	325.292	0.395	128.851
20	5-Me,7-COOH	Tetrazole	13	5.886	8	0.451	0.163	353.766	0.391	145.379
21	5-Cl,7-COOH	Tetrazole	11	5.958	8	0.474	0.163	374.863	0.399	137.55
22	6-Me, 7-COOH	Tetrazole	3.4	6.484	8	0.406	0.163	341.239	0.373	149.384
23	H	COOH	11	6.958	4	0.186	0.167	282.874	0.439	116.634
24	7-COOH	COOH	6.6	6.181	6	0.29	0.167	282.874	0.439	116.634
25	7-COOH	1-Me- Tetrazole	34	5.468	8	0.506	0.163	321.729	0.419	133.036
26	7-CONH *i*-Pr	Tetrazole	5.4	6.264	8	0.214	0.161	361.525	0.317	156.574
27	7-CH_2OH	Tetrazole	4.5	6.346	7	0.375	0.165	297.485	0.402	131.123
28	7-CH_2OMe	Tetrazole	6.0	6.221	7	0.375	0.164	310.649	0.433	150.532
29	7-CH_2NMe_2	Tetrazole	24	5.619	7	0.211	0.163	288.295	0.427	143.164
30	7-Me	Tetrazole	3.3	6.481	6	0.252	0.167	241.855	0.396	127.086
31	7-CH_2COOEt	Tetrazole	2.5	6.602	8	0.319	0.161	402.159	0.416	187.565
32	7-OH	Tetrazole	11	5.958	7	0.421	0.167	272.539	0.374	123.006
33	7-CH_2COOH	Tetrazole	28	5.551	8	0.231	0.171	267.6	0.391	122.891

[a] Concentration of 50 % antihypertensive activity data against Angiotensin II-AT_1 receptor

[b] Negative logarithm of IC_{50}

Statistical analysis

Sequential multiple linear regression (SMLR) analysis was carried out to develop QSAR model. In sequential multiple regression the program searched for all permutation and combination sequentially for the data set. The data was transferred to the statistical program (VALSTAT) in order to establish the correlation between physiochemical descriptors as independent variable and angiotensin antagonistic activity as dependent variable. The ±data within the parentheses are the standard deviation, associated with the coefficient of descriptors in regression equations. Statistical quality of SMLR equation were judges by parameter like observed squared correlation coefficient (r^2), standard error of estimate (SE), sequential Fischer test (F), bootstrapping squared correlation coefficient (r^2_{bs}), bootstrapping standard deviation (S_{bs}), chance statistics evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation, outliers on the basis of Z-score value.

Validation of QSAR model

The best way to evaluate the quality of the regression model is internal validation of QSAR model. Mostly Leave-One-Out (LOO) cross validation, one object (one biological activity value) is eliminated from the training set and training dataset is divided into subsets (number of subsets = number of data points) of equal size. The model is build using these subsets and the predictand (dependent variable) value of the datapoint that was not included in the subset is determined, this is the predicted value. Mean of predicted will be same for r^2 and LOO q^2 (cross validated correlation coefficient value) since all the data point will be sequentially considered as predicted in the LOO subset[17]. Same procedure is repeated after elimination of another object until all objects have been eliminated once. To calculate q^2 following equation was used.

$$q^2 = 1 - \Sigma (Y_{pred} - Y_{act})^2 / \Sigma (Y_{act} - Y_{mean})$$

where Y_{pred}, Y_{act}, and Y_{mean} are predicted, actual and mean values of the pIC_{50} respectively. $\Sigma (Y_{pred} - Y_{act})^2$ is the predictive residual error sum of squares (PRESS).

Statistically, models were validated successfully by parameter like standard deviation of prediction PRESS (S_{press}). The PRESS procedure is equivalent to Leave-One-Out (LOO) cross-validation, as described previously The PRESS statistic is defined as

$$PRESS = \sum_{i-1}^{n} \hat{e}_{(i)}^2$$

$\hat{e}_{(i)}$ is the residual for observation i computed as the difference between the observed value of the predictand and the prediction from a regression model calibrated on the set of n −1(i) observations from which observation i was excluded. Standard deviation of error of predictions (S_{DEP}) it is described as

$$S_{DEP} = \sqrt{} (PRESS/n)$$

Internal consistency of the model is supported by S_{PRESS} and S_{DEP}. These values are calculated from LOO cross validation. Lower values of these parameters describe the better predictability of this model. Bootstrapping analysis was performed for further access of the robustness and statistical confidence. In bootstrapping analysis sub-samples of the data were repetitively analyzed. Each sub-sample is a random sample with replacement from the full sample. One data point can be represented more than once or not at all, but the total number of data points should remain constant. The bootstrapping analysis gives an overview about the contribution of individual molecules to the QSAR model. The R^2_{bs} (bootstrapping squared correlation coefficient) is the average squared correlation coefficient calculated during the validation procedure that is computed from a subset of data points used one at a time for the validation procedure bootstrapping squared correlation coefficient (R^2_{bs}). Bootstrapping standard deviation is the standard deviation of R^2 values of bootstrapping in multiple run of a given data set.

$$SN = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (x_i - \bar{x})^2}$$

where N is the number of bootstrapping (1000 in VALSTAT), $xi = R^2$ value of individual bootstrap and x is the mean of R^2 value of individual bootstrap (R^2_{bs}).

Results and Discussion

QSAR analysis carried out in order to explore properties of the molecules which are responsible for the interaction of molecules with AT_1 receptor. All the descriptor values were calculated from the program (Dragon) were considered as independent variable. Sequential multiple linear regression analysis method was used to develop multi-variant QSAR equation.

pIC_{50}= [7.005(± 1.121)] +nHAcc [-0.410(± 0.150)] +G1s [-4.191(± 2.521)] +Ap [0.017(± 0.006)] .....(1)

n =33, r =0. 779, r^2= 0. 597, SE = 0.331, F = 14.527

pIC_{50}= [7.234(± 1.0463)] +nHAcc [-0.537(± 0.152)] +E3u [4.389(± 2.509)] +E3s [-4.908(± 1.80)] +Vs [0.006 (± 0.002)] .....(2)

Figure (1 & 2)

n =33, r = 0. 825, r^2= 0. 680, SE = 0. 297, F = 17.314

Where n is the number of compounds, r is the correlation coefficient which measures the quality of fit of the model, r^2 is the squared correlation coefficient used to describe the goodness of fit of the data, SE is the standard error of estimation the square root of the variance and measure of the magnitude of the residuals, accounting for accuracy, F is the Fischer ratio values between the variances of calculated and observed activities which is used to measure the levels of the statistical significance of the regression model.

Equations 2 explain for more than 68% variance in activity yet the fitness of Eq^n 2 is more as compare to the Eq^n 1 as shown by value of Fischer sequential test. The model (Eq^n 2) is used for internal predictivity, the value of leave one out cross (LOO) validation squared correlation coefficient (q^2 = 0.659) suggested goodness of the. The model showed overall internal statistical significance level better than 99.9% as it exceeded the tabulated $F_{(4, 33\ \alpha\ 0.001)}$ =17.314 and a significantly low standard error of estimation (SE = 0.297). The model was further tested for outlier by Z-score method and no compound was found to be an outlier prediction. Equation 2 was screened on the basis of inter correlation within the descriptors < 0.43 as mentioned in Table 3.

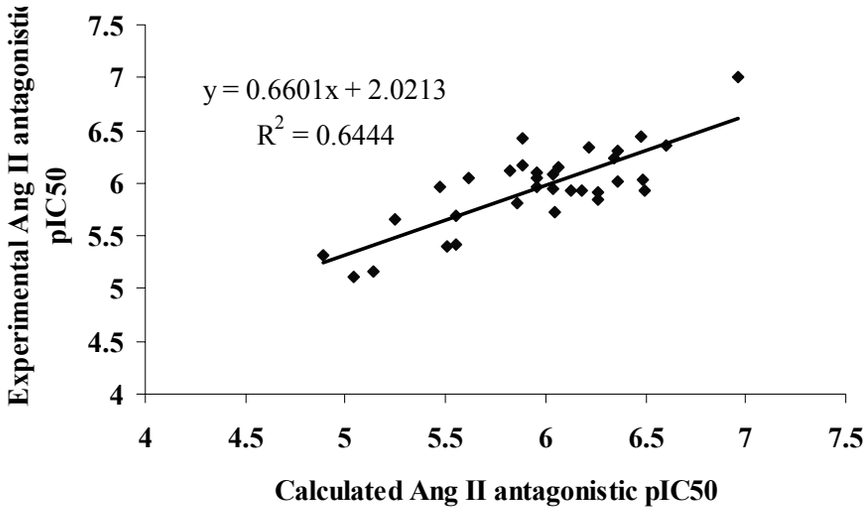


Fig. 1 Plot of the calculated and experimental Ang II pIC50 values using model-2

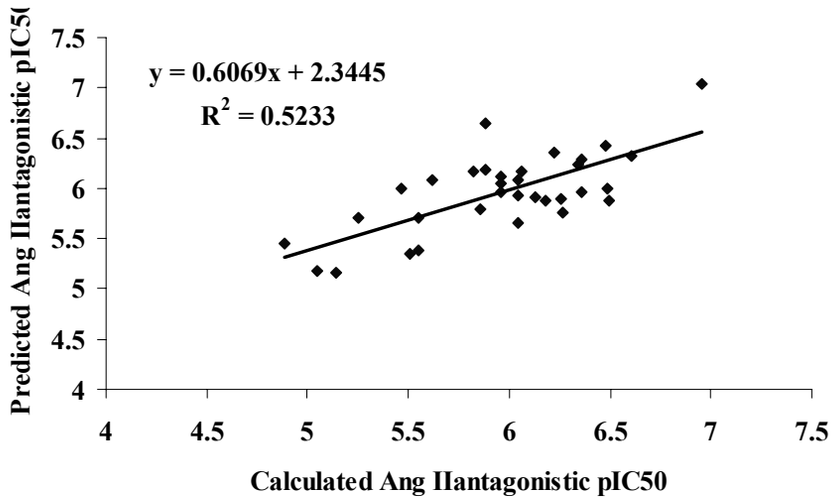


Fig. 2 Plot between experimental and predicted (LOO) Ang II pIC50 values using model-2

To ascertain the predictivity of the model, internal validation using leave one out cross validation process, bootstrapping technique and randomization test were performed. The satisfactory values of internal validation, cross validated squared correlation coefficient (r^2_{cv}) > 0.65, standard deviation of prediction (S_{press}) = 0.343, standard deviation of error of predictions (S_{DEP}) = 0.322, bootstrapping squared correlation coefficient (r^2_{bs}) = 0.697 and chance correlation < 0.01 in the randomize biological activity test revealed that the result were not based on chance correlation. The model's r^2_{cv} > 0.65 supported the predictive ability and significance of the model.

Equation 2 revealed that weighted holistic invariant molecular (WHIM) descriptors like E3u (3rd component accessibility directional WHIM index/unweighted) and Vs (V total size index/weighted by atomic eletrotopological states) contributed positively. A set of 99 WHIM descriptors obtained as statistical indices of the atoms projected onto the three principal components (x, y and z-coordinates of a 3D structure of the molecule) usually from a spatial conformation of minimum energy, within different weighing scheme in a straightforward manner and represent a general approach to describe a molecule in a unitary conceptual framework. The WHIM descriptors are

built in such a way as to capture the relevant molecular 3D information regarding the molecular size, shape, symmetry, and atom distribution with respect to some invariant reference frame. The six different weighting schemes are used for the weighted covariance matrix: u (unweighted), m (atomic mass), p (atomic polarizability), v (Van der Waals volume), e (atomic electronegativity) and s (atomic eletrotopological state)[18, 19].

Table 2 Calculated and predicted pIC_{50} (by LOO method) values with residual and Z-score value using model-2.

Comp. No.	Experimental	Calculated	$Cal._{Res.}$	Z Score	Predicted	$Pred._{Res}$
1	6.045	5.7242	0.3208	1.14921	5.66164	0.38336
2	6.04	6.08397	-0.04397	-0.15752	6.08694	-0.04694
3	5.958	6.04359	-0.08559	-0.306606	6.04698	-0.08898
4	5.823	6.12418	-0.30118	-1.07893	6.16545	-0.34245
5	5.508	5.39189	0.11611	0.415941	5.34718	0.16082
6	5.552	5.6972	-0.1452	-0.520159	5.70817	-0.15617
7	5.142	5.15947	-0.01747	-0.0625856	5.16271	-0.02071
8	6.13	5.93598	0.19402	0.695046	5.90878	0.22122
9	6.3565	6.30102	0.05548	0.198729	6.29428	0.06222
10	6.498	5.92358	0.57442	2.05775	5.88653	0.61147
11	6.06	6.15904	-0.09904	-0.354811	6.17192	-0.11192
12	6.356	6.01255	0.34345	1.23037	5.96965	0.38635
13	6.04	5.94972	0.09028	0.323422	5.93236	0.10764
14	4.886	5.30658	-0.42058	-1.50665	5.45548	-0.56948
15	5.856	5.80242	0.05358	0.191954	5.78631	0.06969
16	5.886	6.4176	-0.5316	-1.90435	6.64997	-0.76397
17	5.25	5.64802	-0.39802	-1.42584	5.70276	-0.45276
18	5.045	5.11637	-0.07137	-0.255654	5.17448	-0.12948
19	6.259	5.91101	0.34799	1.24661	5.88863	0.37037
20	5.886	6.16096	-0.27496	-0.984981	6.18631	-0.30031
21	5.958	6.10155	-0.14355	-0.514252	6.11178	-0.15378
22	6.484	6.03862	0.44538	1.59551	6.00295	0.48105
23	6.958	6.99681	-0.03881	-0.139013	7.03326	-0.07526
24	6.18	5.92134	0.25866	0.926591	5.88538	0.29462
25	5.468	5.95551	-0.48751	-1.74642	5.98968	-0.52168
26	6.264	5.84685	0.41715	1.49438	5.75256	0.51144
27	6.346	6.23725	0.10875	0.389576	6.22923	0.11677
28	6.221	6.34051	-0.11951	-0.428131	6.35038	-0.12938
29	5.619	6.04169	-0.42269	-1.5142	6.07668	-0.45768
30	6.481	6.4397	0.0413	0.147811	6.43078	0.05022
31	6.602	6.3584	0.2436	0.872671	6.32874	0.27326
32	5.958	5.96586	-0.00786	-0.0281466	5.96638	-0.00838
33	5.55	5.41027	0.13973	0.500576	5.3888	0.1612

Table 3 Inter-correlation matrix of descriptors used in model-2.

Parameter	nHAcc	E3u	E3s	Vs
nHAcc	1.000000			
E3u	0.203631	1.000000		
E3s	0.290985	0.401926	1.000000	
Vs	0.432266	0.295822	0.105337	1.000000

QSAR models were obtained in this study using the WHIM descriptors weight by the atomic eletrotopological state (s) and by unweighted scheme (u). Descriptors like E3s (3^{rd} component accessibility directional WHIM index/ weighted by atomic eletrotopological states), nHAcc (number of acceptor atom for H-bonds), contributed negatively to the model. Structural investigation revealed that the Ang II antagonistic activity is predominantly explained by substituent molecular size, shape and atom distribution and provided insights into how modulation of eletrotopology of substituents could be useful to optimize Ang II antagonistic activity.

Conclusion

In this study, WHIM descriptor was used to predict the activity for a series of compounds (substituted benzimidazole). The QSAR model developed in the present work is easily calculated and suitable for the rapid prediction of Ang II antagonistic activity of substituted benzimidazole derivatives, and the cross-validation of the QSAR model supports this claim. The WHIM descriptors are becoming an attractive tool for efficient drug design process. Its usefulness is proven here in QSAR analysis. WHIM descriptors had a good coefficient of correlation (q^2 LOO) and showed a minor standard error of estimation (SE) for series of compounds. We considered that WHIM descriptors can be a very useful tool for the prediction of Ang II antagonistic activity of substituted benzimidazole series.

Acknowledgment

Authors are thankful to Prof. Arun Gupta, SCOPE, Indore, MP, India for his valuable suggestions and support to complete this work.

References

[1] Vallotton, M.B. Trends Pharmacol. Sci.1987, 8, 69.

[2] Zaid, A.; Winaver J.; Feuerste G.Z. Biochem. Pharmacol. 2009**,** 78, 933.

[3] Corvol, P. Clin. Exp. Hypertens. 1989, *A11*, 463.

[4] Gavras, H.; Brunner, H.R.; Turini, G.A.; Kershaw, G.R.; Tifft, C.P.; Cuttelod, S.; Gavras, I.; Vukovich, R.A.; McKinstry, D.N. N. Eng. J. Med. 1978, 298, 991.

[5] De Gasparo, M.; Catt, K. J.; Inagami, T.; Wright, J.W.; Unger, T. Pharmacol. Rev. 2000, 52, 415.

[6] Captopril Multicenter Research Group. J. Am. Co.11 Cardiol. 1983, 2, 755.

[7] The SOLVD Investigators. N. Engl. J. Med. 1991, 325, 293.

[8] Case, D.B.; Atlas, S.A.; Marion, R.M.; Laragh, J.H. Am. J. Cardiol. 1982, 49, 1440.

[9] Lew, M.J.; Ziogas, J.; Christopoulos, A. Sciences 2000, 21, 376.

[10] Carini, D.J.; Duncia, J.V.; Aldrich, P.E.; Chiu, A.T.; Johnson, A.L.; "Pierce, M.E.; Price, W.A.;" Snatella, J.B.; "Wells, G.J.; Wexler, R.R.;" Wong, P.C.; Yoo, S.E.; Timmermans, P.B.M.W.M. J. Med. Chem. 1991, 34, 2525.

[11] Kubo, K.; Yasuhisa, K.; Imamiya, E.; Yoshihiro, S.; Inada, Y.; Furukawa, Y.; Nishikawa, N.T. J. Med. Chem. 1993, 36, 2182.

[12] Ries, U.J.; Mihm, G.; Narr, B.; Hasselbach, K.M.; Wittneben, H.; Entzeroth, M.; Van Meel J.C.; Wienen W.; Hauel N.H. J. Med. Chem. 1993, 25, 4040.

[13] Kubo, K.; Yasuhisa, K.; Imamiya, E.; Yoshihiro, S.; Inada, Y.; Furukawa Y.; Nishikawa, N. T. J. Med. Chem. 1993, 36 , 1772.

[14] Chem Draw ultra 8.0, 2004, Version 8.0, Cambridge soft Corporation 1986-2005, software publishers association, 1730 m Street, suite 700, Washington DC 20036, USA.

[15] Todeschini, R.; Consonni, V. DRAGON-Software for the calculation of molecular Descriptors, rel. 1.12 for Windows, 2001.

[16] Gupta, A.K.; Arokia, B.M.; Khakhedikar, S.G. Indian J. Pharm. Sci. 2004, 66, 396.

[17] Kubyani H. Quant. Struct. Act. Relat.1994, 13, 285.

[18] Todeschini, R.; Gramatica, P. Quant. Struct .Act. Relat. 1997, 16,113.

[19] Todeschini, R.; Vighi, M.; Finizio, A.; Gramatica, P. SAR & QSAR Environ. Res.1997, 7, 173.