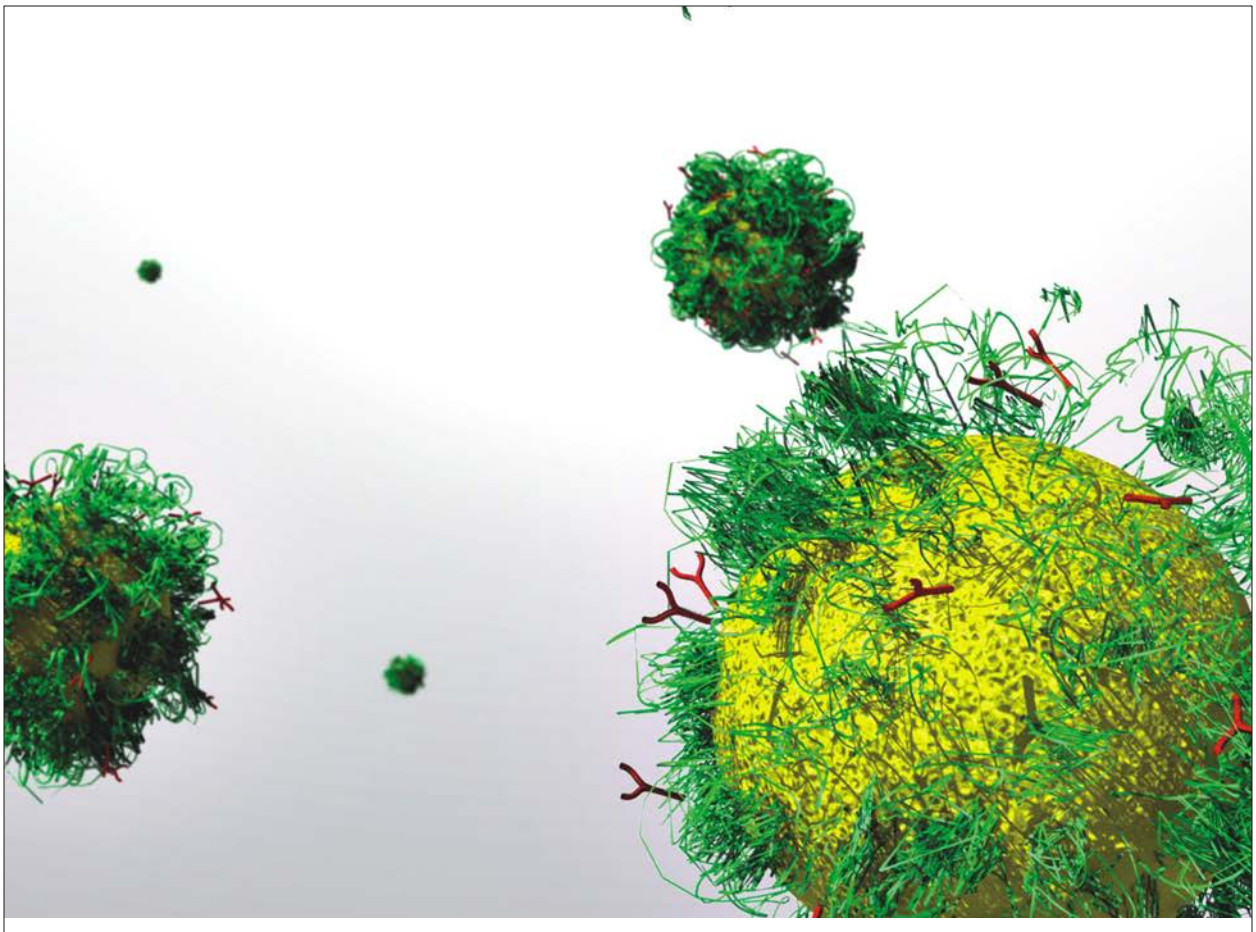


American Journal of Drug Discovery and Development

ISSN 2150-427X

Academic Journals Inc.

www.academicjournals.com

American Journal of Drug Discovery and Development 1 (2): 85-104, 2011
ISSN 2150-427x / DOI: 10.3923/ajdd.2011.85.104

Quantitative Structure Activity Relationship Analysis of N-(mercaptoalkanoyl)- and [(acylthio)alkanoyl] Glycine Derivatives as ACE Inhibitors

[1]Sarvesh Kumar Paliwal, [1]Anubhuti Pandey and [2]Shailendra Paliwal
[1]Department of Pharmacy, Banasthali University, Banasthali, Tonk-304022, Rajasthan, India
[2]Department of Pharmacy, L.L.R.M. Medical College, Meerut, U.P., India

Corresponding Author: Sarvesh Kumar Paliwal, Department of Pharmacy, Banasthali University, P.O. Banasthali Vidyapith, Tonk, Rajasthan- 304022, India Tel: +91-1438-228341/348 Fax: +91-1438-228365

ABSTRACT

Angiotensin Converting Enzyme (ACE) inhibitors have been acknowledged as the first-line agents for the treatment of hypertension and a variety of cardiovascular disorders. The present study aims to develop Quantitative Structure-Activity Relationship (QSAR) models for a series of N- (mercaptoalkanoyl)- and [(acylthio)alkanoyl]glycines derivatives for the prediction of the activity of novel compounds as ACE inhibitors. Multiple Linear Regression (MLR) and Partial Least Square (PLS) analyses were used to establish the QSAR between ACE inhibitory activities and molecular descriptors. The models generated by MLR and PLS analyses were comparable and demonstrated good predictive ability with statistical values of $R^2 = 0.76$, F = 33.35 and s = 0.328 for MLR and statistical significance value of 0.536 and fraction of variance explained = 0.733 for PLS analysis. Cross-validated R^2 values of 0.706 (for MLR) and 0.712 (for PLS) were obtained which indicates good internal predictive capacity of the models. Validation through external test set provided R^2 values of 0.698 and 0.726 for the MLR and PLS analyses, respectively. The results obtained indicate the importance of steric (Verloop B1, K-alpha 3) hydrophobic (lipole Z component) and topological (Wiener index) descriptors in determining the activity of ACE inhibitors. Also, druggability of the compounds was checked by assessing the Lipinski's rule of five and no violation to this rule was found. The utility of this study is for the effective design of novel, more potent ACE inhibitors as it provides important information about the geometrical and structural requirements for the interaction of glycine derivatives with ACE.

Key words: Angiotensin-converting enzyme inhibitors, multiple linear regression, partial least square, quantitative structure-activity relationship, TSAR

INTRODUCTION

The Renin-Angiotensin System (RAS) is pivotal in the regulation of blood pressure and electrolyte balance. Angiotensin-Converting Enzyme (ACE) plays a crucial role in the RAS by the production of a potent vasoconstrictive octapeptide angiotensin II which affects peripheral resistance, renal function and cardiovascular structure (Jackson, 2001).

ACE is a chloride-dependent zinc metallopeptidase that contains 1277 amino acid residues and has two homologous domains, each with a catalytic site and a region for binding Zn^{++}. It is non-specific and cleaves dipeptide units from substrates with diverse amino acid sequences.

Bradykinin is one of the many natural substrates for ACE, whose inactivation by ACE further contributes to hypertension (Kuoppala *et al*., 2000). The myocardium of failing heart in patients of heart failure shows increased levels of ACE mRNA, ACE protein and ACE activity (Wright *et al*., 2008).

Over-stimulation of the RAS causes an increase in blood pressure, blood volume and changes in cardiac and vascular structure. If this continues for a long time, may lead to excessive vasoconstriction, fibrosis and cardiac remodeling. If untreated, there may be a chain of events, progressing through a number of physiological steps, including atherosclerosis to Left Ventricular Hypertrophy (LVH) coronary thrombosis, myocardial infarcts to heart failure in the end (Wright *et al*., 2008).

Since the development of first marketed ACE inhibitor, captopril, these agents have become the first-line agents for the treatment of hypertension and a variety of cardiovascular disorders including heart failure, left ventricular hypertrophy, post myocardial infarction, chronic kidney diseases (including diabetic and non-diabetic nephropathy) and proteinuria (Sutters, 2008). As a summary of evidence from clinical trials, it is reported that treatment with ACE inhibitors has a beneficial role in patients selected for the treatment of left ventricular dysfunction after Acute Myocardial Infarction (AMI) and in relatively unselected patients with AMI (Latini *et al*., 1995). Several clinical trials have been performed to study the beneficial effects of ACE inhibitors on diabetes mellitus induced AMI and it was found that apart from the beneficial effects in vascular remodeling, they also reduced recurrent ischemic events after myocardial infarction (Nesto and Zarich, 1998). ACE inhibitors are more effective than any other antihypertensive drug in treating chronic renal diseases, even in normotensive patients (Fogo, 1999). ACE inhibitors are also suggested to be used in patients with diabetic nephropathy. It is reported that ACE inhibitors significantly retard the development of end-stage renal failure compared to other antihypertensives, particularly in patients with proteinuria below the median (Yokoyama *et al*., 1997). A brief report of a patient with congenital nephrotic syndrome (development of nephrotic syndrome in the first three months of life) of unusual etiology suggested responsiveness to an ACE inhibitor alone (captopril) (Shreedharan and Bockenhauer, 2005). A brief review of literature cited above clearly shows the superiority of ACE inhibitors for the treatment of cardiovascular diseases.

Since its advent, the Quantitative Structure Activity Relationship (QSAR) technique (Hansch and Fujita, 1964) has been widely employed in modeling biological activities as well as ADME/Toxicity properties. QSAR models are mathematical equations which try to correlate the structural and chemical characteristics of drug molecules with their biological activities. Once the relationships are established, the information helps in rationally designing more potent compounds and the predictions of biological activities can be done for many new compounds, as suggested by several researchers (Jamloki *et al*., 2006; Abhilash *et al*., 2006; Karthikeyan *et al*., 2006; Jain and Chaturvedi, 2008). QSAR studies are of great value in the study of enzyme inhibition in determining the mechanism of inhibition and identifying the important active sites in the receptor. These aspects of QSAR studies become of paramount importance in drug design (Gupta and Kumaran, 2006). Recently, QSAR studies have been successfully applied to guide the design of potent new compounds as anti-HIV (Karthikeyan *et al*., 2007; Thakur *et al*., 2007) and anti-cancer agents (Moorthy and Trivedi, 2006).

Various N-substituted (mercaptoalkanoyl)- and [(acylthio)alkanoyl] amino acids derivatives have been designed, synthesized and evaluated *in vitro* and *in vivo* as ACE inhibitors

(Panday *et al.*, 2009). One of the active member of the series of compounds used in the present study is (S)-N-cyclopentyl-N-[3-[(2,2-dimethyl-1-oxopropyl)thio]-2-methyl-1-oxopropyl]glycine (pivopril or pivalopril) having potency lower than that of captopril (Kumar *et al.*, 2010). This prompted us to further explore glycine based ACE inhibitors.

We preferred simple and less error prone 2D QSAR approach to 3D QSAR. 2D is more beneficial compared to 3D QSAR methods, as it neither requires conformational search nor structural alignment (Shen *et al.*, 2002; Hoffman *et al.*, 1999). Moreover, 2D methods also have some intrinsic advantages such as, structural key type descriptors which implicitly encode much chemical information that might otherwise be difficult to explicitly calculate (Rogers and Hopfinger, 1994). Several studies support the superiority of 2D over 3D methods (Hoffman *et al.*, 1999; Bajorath, 2005; Zheng and Tropsha, 2000; Golbraikh *et al.*, 2001). Also, 2D QSAR methods are easily automated and adapted to the task of database searching or virtual screening (Tropsha *et al.*, 1999).

MATERIALS AND METHODS

The experiments were done at Banasthali University, Rajasthan by Anubhuti Pandey as part of her M.Sc. project during January 2009 to June 2009.

Generation and 3-dimensional optimization of chemical structures: The chemical structures of 63 derivatives of N-substituted (mercaptoalkanoyl)- and [(acylthio)alkanoyl] glycines (Appendix Table A1) were sketched using standalone module of Discovery Studio 2.0. Compound 23a and 74a, being racemic mixtures, were excluded. Also compound 74b was avoided due to its uncertain IC_{50} value. The structures were then, imported into the worksheet of TSAR (version 3.3; Accelrys Inc., Oxford, England).

The series consisted of three substitutions that were defined using "define substituent" option in the TSAR worksheet's toolbar. The understanding of the molecular properties or ligand-receptor interactions requires not only information on how atoms are connected in a molecule (connection Table) but also on their 3D structure. The structures and their substituents were converted from 2D to 3D using CORINA. CORINA is a method for predicting 3D-coordinates directly from the structural formula of the molecule. It generates by default one low energy conformation for each input structure and all structures that can be expressed in a valence bond notation can be expressed. Stereochemical information is also considered and rings and chains are considered separately (Sadowski and Gasteiger, 1993).

Partial atomic charges of the molecules were calculated using "Charge 2 - derive charges" option. Deriving partial charges is a prerequisite for several structural manipulations, such as optimizing a 3D model and for many property calculations.

Further, 3D optimization of the structures was done using COSMIC (Vinter *et al.*, 1987). The components of the COSMIC parameters are valance terms (including bond potentials, bond angle potentials and torsional potentials) and non-bonded terms (including electrostatic interactions and Van der Waals interactions). Total molecular energies were calculated using COSMIC by summing bond length, bond angle, torsion angle, Van der Waals and coulombic terms for all appropriate sets of atoms. The force field supplied by COSMIC for energy calculations during a flexible optimization, ensures that only the more energetically realistic conformations are considered.

Table 1: Molecular descriptors employed in present QSAR study

Atomic attributes	Molecular surface area, molecular volume, molecular mass, Verloop steric parameters (calculated only for the substituents) inertia moment size and length, total dipole, dipole moment components, substituent bond dipole, log P, total lipole, lipole components, substituent bond lipole, molar refractivity.
Molecular indices	Connectivity indices, shape indices, topological indices.
Atom counts	H bond donors, H bond acceptors.
VAMP electrostatic properties	Total energy, electronic energy, nuclear repulsion energy, accessible surface area, overall atomic charges, mean polarizability, heat of formation, HOMO eigen value, LUMO eigen value, ionization potential, total dipole, polarizability components.

Calculation of descriptors and collection into QSAR data table: The experimentally determined IC_{50} values of the 63 compounds taken from the literature (Suh *et al.*, 1985) (Appendix Table A1) were converted into the negative logarithm (log $1/IC_{50}$) and were imported into the worksheet to be used as dependent variables. More than 188 molecular descriptors were calculated for use in the QSAR modeling studies, using TSAR software programs. The calculated descriptors included molecular attributes, molecular indices, atom counts and VAMP parameters (Table 1). The TSAR methodology assumes that a suitable sampling of these structural descriptors provides all the information needed for understanding their biological properties (Klocker *et al.*, 2002; Kovatcheva *et al.*, 2003).

Data set preparation and data reduction: The 63 molecules of the series were randomly divided into training set and test set. Training set consisting of 53 molecules was used for Multiple Linear Regression (MLR) and Partial Least Square (PLS) model development and the test set consisting of 10 molecules was used later to check the predictive power of the developed model.

Initially, the descriptors with constant values were discarded. Before model development, the correlation of descriptors with each other was investigated. Among the detected collinear descriptors (i.e., $R^2>0.5$) one of them which had the highest correlation with activity was retained and the rest were removed from the data matrix of descriptors. This was done with the purpose of getting the descriptors that were less correlated to each other, as high co-linearity among descriptors can lead to statistical instability, over-prediction and also makes mechanistic interpretation difficult. The reduced set of molecular descriptors was used as independent variables in the regression analysis to establish the quantitative structure-activity relationship.

Model development and validation: The Multiple Linear Regression (MLR) was carried out to derive best QSAR models. Various MLR models were generated using biological activity data as dependent variable and selected descriptors as the independent variables. These models were used to quantify the relationship between dependent Y variables and independent X variables. The models generated in the form of regression equation explain the activity data and can be used to predict the activity of new compounds. Positive values of the regression coefficients indicate that the given descriptor contributes positively to the biological activity, where as negative values indicate that the increase in the value of the descriptor lead to a decrease in the activity value. Statistical significance of the regression equations are tested on the basis of conventional regression coefficient (R^2) Fischer statistic (F) and the standard deviation (s).

The models obtained were validated using both internal and external validation techniques. Internal validation was performed by applying cross-validation analysis using Leave-One-Out(LOO) method in which one molecule is removed from the training set and the model is

recalculated. The predicted activity for that molecule is then compared with its actual value. This is repeated until each molecule is omitted once. Further, as a method of external validation, the activities of molecules in the test set were predicted using the model developed by the training set.

Partial Least Square (PLS) is a multivariate analysis based on principal component analysis. This technique carries the generation of principal components and the multiple regression in a single step and in addition gives maximal correlation between the principle components (independent variables) and the dependent variable. The linear equation obtained as a result of PLS analysis Eq. 2 indicates the relationship between a dependent (activity) variable Y and independent variables X which are latent variables or principal components. Positive and negative values of the coefficients of independent variables signify their positive or negative effect to the biological activity. PLS has been recommended as an alternative approach to enlarge the information content in each model and avoid danger of over-fitting (Kubinyi, 1996). As an approach to check the robustness and the predictive ability of the models generated using MLR analysis, PLS analysis was performed on the same training set of compounds. Models generated using PLS were also validated by LOO method (Vengurlekar *et al.*, 2010).

Assessment of druggability: Knowledge of Absorption, Distribution, Metabolism and Excretion (ADME) provides a mechanistic platform to understand pharmacokinetic and pharmacodynamic relationships of a potential drug compound. There is a significant relationship between the molecular properties and membrane permeability of a compound. With the aim of predicting which compounds are likely to display poor *in vivo* absorption characteristics, we decided to check the violation of the Lipinski's rule of five (Lipinski *et al.*, 1997). According to which, poor oral absorption is more likely when a compound possesses more than five H-bond donors, more than ten H-bond acceptors, clog P (calculated log P) greater than five and molecular weight over 500 Da. Computational assessment of these properties was done with the help of "ADME check" option of the TSAR software.

RESULTS

As an initial approach the MLR model was developed using ten independent molecular descriptors retained after data reduction which were independent to each other and were least inter-correlated. Further, in order to improve the statistical quality of the model, the number of independent descriptors was reduced employing backward elimination using t-values. So, the t-values of all the descriptors were checked keeping the stepping to zero and the less significant variables, having lower t-value were deleted from the model.

The above process helped in the retrieval of seven independent molecular descriptors, Verloop B1 substituent-2, dipole moment X component substituent-2, dipole moment Y component substituent-2, lipole Z component whole molecule, lipole Z component substituent-2, K-alpha3 index whole molecule and Wiener topological index substituent-1, having good correlation with the biological activity and minimum intercorrelation. The model developed with seven descriptors showed the statistical values of $R^2 = 0.564$, s = 0.501, F = 15.537 and R^2 (CV) = 0.437 (Table 2). These descriptors were used to perform the stepwise multiple linear regression analysis. In stepwise regression, the independent variables were correlated in a stepwise manner with the dependent variable. With stepping 4, Verloop B1 substituent-2, lipole Z component whole molecule, K-alpha 3 index whole molecule and Wiener topological index substituent-1 entered into the model while dipole moment X component substituent-2, dipole moment Y component substituent-2 and lipole

Z component substituent-2 were excluded from the model. On deleting these three descriptors we arrived to a model with comparatively improved statistical values of R^2 = 0.590, s = 0.444, F = 17.266 and R^2 (CV) = 0.500 (Table 2). For the model generated with four descriptors, graph was plotted between the actual activity and the predicted activity of the training set of compounds (Fig. 1). In the plotted graph, it was observed that certain molecules are fitted far apart from the regression line. These compounds were identified as the potential outliers. The outliers may point toward an incorrectly measured experimental value, a different binding conformation, a significant difference in the physicochemical properties, or structural uniqueness (Liao *et al*., 2004). After deleting six outliers (16, 38, 40, 32, 53 and 56) and cross validation with leave out one row, the best model was generated that included four parameters Verloop B1 substituent-2, Lipole Z component whole molecule, K-alpha3 whole molecule and Wiener topological index substituent-1. The descriptors included in the final QSAR model and their statistical significance is given in Table 3. The t-values for the parameters are greater than 2 which indicate their significance in the model. The correlation between biological activity and parameters used is given in Table 4.

The QSAR equation generated from training set using MLR analysis clearly show the importance of descriptors selected in the present study.

$$Y = 0.907*X1 + 0.069*X2 - 0.208*X3 - 0.037*X4 + 0.359 \quad (1)$$

n = 47, r = 0.872, R^2 = 0.761, R^2 (CV) = 0.706, F = 33.35, s = 0.328, Residual sum of square = 4.516, Predictive sum of square = 5.537

Table 2: Statistical test values of the models developed by MLR analysis

	s (a)	F (a)	R^2 (a)	R^2(CV) (a)
Model generated with 7 descriptors (before deleting the outliers)	0.501	15.537	0.564	0.437
Model generated with 4 descriptors (before deleting the outliers)	0.444	17.266	0.590	0.500
Model generated with 4 descriptors (after deleting the outliers)	0.328	33.354	0.761	0.706

(a) s: Standard deviation, F: Fischer statistic, R^2: Regression coefficient, R^2 (CV): Cross-validation regression coefficient

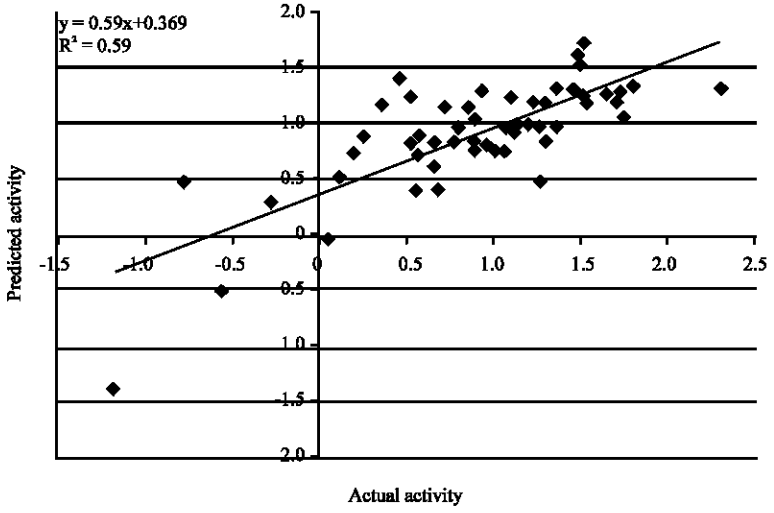


Fig. 1: Actual vs predicted activity for the training set of compounds (including outliers) derived from MLR analysis

where, X1 is Verloop B1 substituent-2, X2 is Lipole Z component whole molecule, X3 is K-alpha3 index whole molecule and X4 is Wiener topological index substituent-1.

In the above-mentioned equation, the value of R^2 is 0.761 which means that the equation accounts for 0.761×100 = 76.1% variance in biological activity which is clearly quite a reasonable fit.

The cross-validation regression coefficient, R^2(CV) is 0.706 (higher than 0.6) and there is small difference between R^2 and R^2(CV) indicating good internal predictive ability of the developed model. These statistical values are given in Table 2.

F is the Fischer statistic, a measure of the probability that the correlation has not occurred by chance. The F-test reflects the ratio of variance explained by the model and the variance due to the error in the regression. The value of F-test (= 33.35) was also found to be significant. Standard deviation is measured by the error mean square which expresses the variation of the residuals or the variation about the regression line. Thus, standard deviation is an absolute measure of quality of fit of the model. It should have a low value for the regression to be significant. The value of standard deviation is 0.328 which is low.

To confirm the soundness and predictive ability of the model, PLS analysis was performed using the same data set. For a well defined problem, both MLR and PLS should have comparable results (Paliwal *et al.*, 2009, 2010). The results of the PLS analysis as shown in Eq.2 were also evaluated on the basis of R^2(CV) and statistical significance of the model.

$$Y = 0.408*X1 + 0.060*X2 - 0.201*X3 - 0.041*X4 + 1.240 \quad (2)$$

n = 47, Statistical significance = 0.536, R^2(CV) = 0.712, Fraction of variance explained = 0.733, Residual sum of square = 12.284, Predictive sum of square = 13.233 (Table 5).

Table 3: Statistical significance of parameters in the best QSAR model obtained by MLR

Parameter	Coefficient[a]	Jackknife SE[b]	Covariance SE[c]	t-value[d]
Verloop B1 (subst 2)	0.90687	0.26087	0.2592	3.4987
Lipole Z component (whole molecule)	0.06903	0.014995	0.014752	4.6793
K-alpha3 index (whole molecule)	-0.20766	0.041183	0.041564	-4.9962
Wiener Topo. Index (subst 1)	-0.037258	0.008293	0.0074902	-4.9743

[a]The regression coefficient for each variable in the equation, [b]An estimate of the standard error on each regression coefficient derived from the jack-knife procedure on the final regression model, [c]Gives an estimate of the standard error on each regression coefficient derived from the covariance matrix, [d]Measures the significance of each variable included in the final model

Table 4: Correlation matrix showing correlation between biological activity and parameter used

	Log ($1/IC_{50}$)	Verloop B1 substituent-2	Lipole Z component whole molecule	K-alpha3 index whole molecule	Wiener topological index substituent-1
Log ($1/IC_{50}$)	1	0.168	0.446	-0.577	-0.670
Verloop B1 substituent-2	0.168	1	0.070	0.102	0.189
Lipole Z component whole molecule	0.446	0.070	1	0.087	-0.208
K-alpha3 index whole molecule	-0.577	0.102	0.087	1	0.455
Wiener topological index substituent-1	-0.670	0.189	-0.208	0.455	1

Table 5: Statistical test values of the model developed by PLS analysis

Statistical significance	Fraction of variance explained	R^2(CV)	Residual sum of square	Predictive sum of square
0.536	0.733	0.712	12.284	13.233

The experimentally determined log ($1/IC_{50}$) values and predicted log ($1/IC_{50}$) values for the training and test set of compounds are given in Appendix Table A2. Graphs plotted between the actual and predicted activity of training (excluding outliers) and test set, obtained as a result of MLR analysis, are shown in Fig. 2 and 3, respectively. Figure 2 shows that a regression coefficient R^2 value of 0.761 was obtained indicating 76.1% variance in biological activity. Figure 3 signifies that R^2 value of 0.698 was obtained for the test set by MLR, suggesting good external validation. Similarly, the graph of actual versus predicted activity of training set (excluding outliers) obtained by PLS analysis (Fig. 4) shows that R^2 value of 0.733 was obtained. This signifies 73.3% variance in biological activity. Figure 5 depicts the plot of actual versus predicted activity of test set of

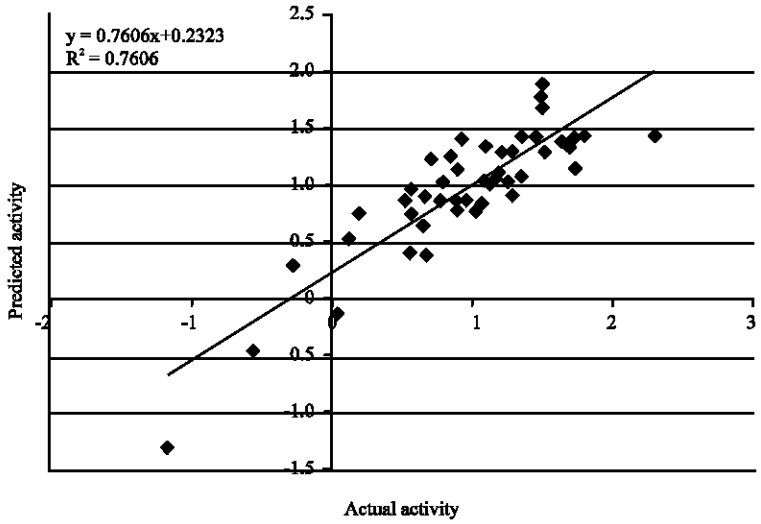


Fig. 2: Actual vs. predicted activity for the training set of compounds (excluding outliers) derived from MLR analysis

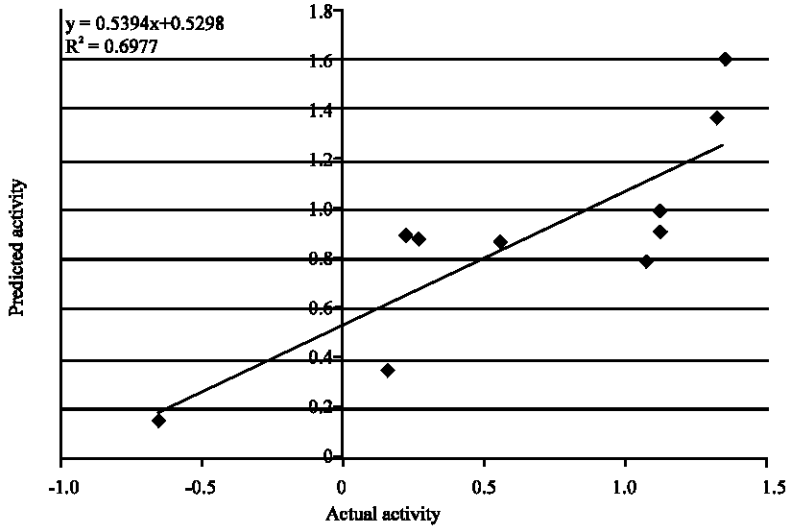


Fig. 3: Actual vs predicted activity for the test set of compounds derived from MLR analysis

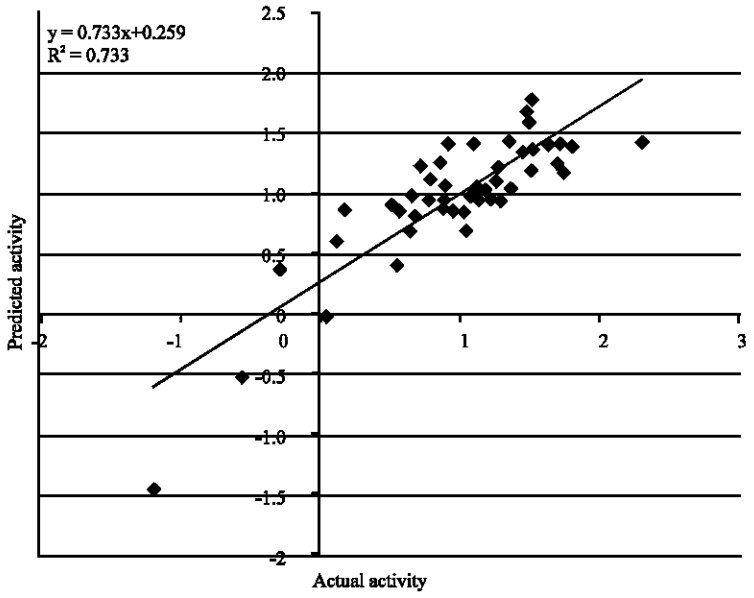


Fig. 4: Actual vs predicted activity for the training set of compounds (excluding outliers) derived from PLS analysis

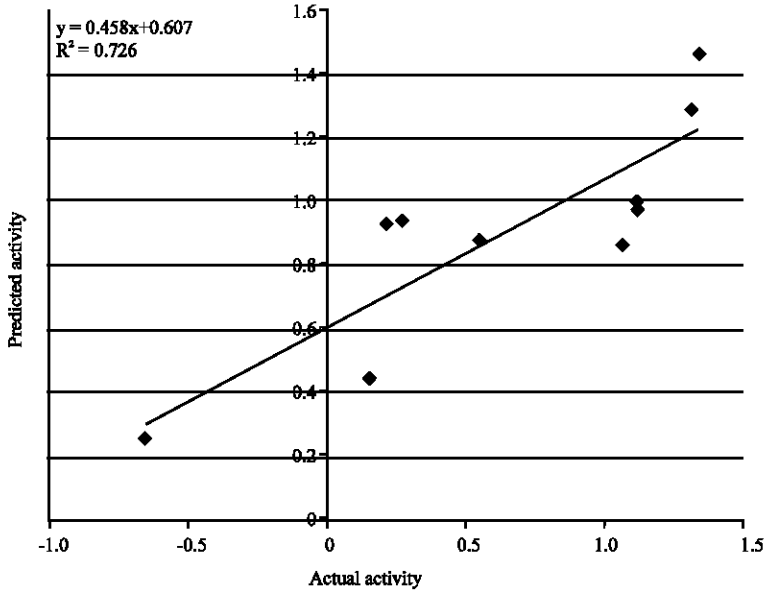


Fig. 5: Actual vs predicted activity for the test set of compounds derived from PLS analysis

compounds, derived from PLS analysis. It displays the R^2 value of 0.726 obtained by PLS analysis, further suggesting good external validation.

DISCUSSION

As the model suggests, ACE inhibitor activity increases with an increase in Verloop B1 parameter of substituent 2 and lipole Z component of the whole molecule and decreases with an

increase in the values of K-alpha3 index for whole molecule and Wiener topological index for substituent 1.

The Verloop parameters (Verloop, 1961) are a set of multi-dimensional steric descriptors that define a box that can be used to characterize the shape and volume of the substituent. These parameters are very important in explaining the steric influence of substituents in the interaction of the drug molecule with the target macromolecule. Verloop B1 is a width parameter defined as the smallest width of the substituent in any direction perpendicular to the length of the substituent. The study suggests that the ACE inhibitory activity is strongly correlated with variations in substitutions at nitrogen, by various alkyl, cycloalkyl, bicycloalkyl, aryl, alkynyl and heterocyclic groups.

The model suggests that there is an absolute requirement of optimum value for lipophilic descriptor, lipole Z component of the whole molecule. Lipole Z component is a directional component of lipophilicity. Any decrease in the value of lipole Z component of whole molecule leads to decrease in biological activity, explaining the importance of lipophilic core and substituents in interaction of glycine derivatives and ACE.

Steric parameter K-alpha 3 index of whole molecule is the third order K-alpha index which can be used to encode the shape of the molecule important for biological activity (Kier and Hall, 1999). As the value for K-alpha 3 index of whole molecules increases, their biological activity decreases.

The fourth descriptor in the regression model is the Wiener topological index (Wiener, 1947). The Wiener index characterizes the "compactness" of a molecule, being larger for extended chains. Here, Wiener index for substituent 1 is negatively correlated to biological activity which signifies that presence of a bulky group at R^1 position is detrimental to the activity, as with compounds 73 and 74c.

All the compounds of the dataset showed no violation of the Lipinski's rule of five (Appendix Table A3) which indicates their potential druggability and good absorption characteristics.

The knowledge on structural requirements for ACE inhibition has been derived from a number of SAR studies (Wyvratt and Patchett, 1985; Mayer *et al.*, 1987). In particular, the following three features required for ACE inhibitor activity has been proposed: (1) a terminal carboxyl group (believed to interact with an arginine residue in the receptor) (2) an amido carbonyl group (with hydrogen bonds to an amide carbonyl in the receptor) and (3) a zinc-binding group (which can be a sulfhydryl, carboxylic acid or a phosphinic acid). This structural information defining the minimal set of active site groups necessary for ACE inhibition has formed the basis for several 3D QSAR studies. These studies have analysed databases of diverse structural classes of ACE inhibitors to determine a common three-dimensional geometry for the active site consistent with their activity (DePriest *et al.*, 1993; Bohacek *et al.*, 1996; Bersuker *et al.*, 2000; San Juan and Cho, 2005).

The model of ACE inhibitor binding suggested by DePriest *et al.* (1993) indicates the importance of hydrophobic and steric interactions. This is in support to our results. Bohacek *et al.* (1996) constructed 3D models to design dual ACE/NEP inhibitors. Their study reveals that even in different zinc metalloproteases, the inhibitor atoms between the zinc binding group and P_1' carbonyl side chain have a common geometry. Present study is in agreement to this postulate as it also reveals the importance of optimum shape and topology especially in the zinc binding domain of the glycine based inhibitors.

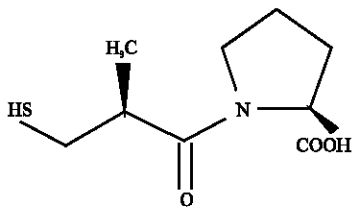


Fig. 6: The chemical structure of captopril

Bersuker *et al.* (2000) proposed an improved electron-conformational method of pharmacophore identification and bioactivity prediction. According to these researchers, in case of many conformations of the same compound only the one having lowest energy, should be parameterized. In this work, we optimized the structures using COSMIC which ensures that during a flexible optimization, only the more energetically realistic conformations are considered. According to Bersuker *et al.* (2000), the active fragment (pharmacophore) responsible for ACE inhibitor activity contains three oxygen atoms and one atom X (X = S, N, O). In addition, their study reveals the presence of hydrophobic auxiliary groups (AG) surrounding the entire inhibitor structures which may attribute to an enhanced inhibitor activity. The model developed in our study is consistent with this study as it also suggests that hydrophobic character of entire molecules is important for an enhanced ACE inhibitor activity.

San Juan and Cho (2005) suggested that steric groups are favoured along the proline ring of the 2-methylpropionyl-Lproline and the sulfonyl group of 3-mercapto moieties of the captopril chemical structure. Furthermore, the presence of electropositive group on the propionyl moiety of captopril as well as hydrophobic group at the sulfonyl moiety is expected to increase activity. Present 2D QSAR study, conducted specifically on glycine based ACE inhibitors is in line to the above findings indicating the importance of steric influence of N- substitutions in interaction of N-(mercaptoalkanoyl)- and [(acylthio)alkanoyl]glycine derivatives and ACE. In addition, the developed model also signifies the importance of optimum shape and hydrophobic character of the entire molecules for an enhanced ACE inhibitor activity. Furthermore, larger group or extended chain substitutions at the sulfhydryl moiety in mercaptopropanoyl glycines are unfavourable to the inhibitor activity. This postulate is also supported by the fact that captopril having a small sulfhydryl moiety as the zinc binding group (Fig. 6) has high ACE inhibitor activity (IC_{50} = 0.017 μM).

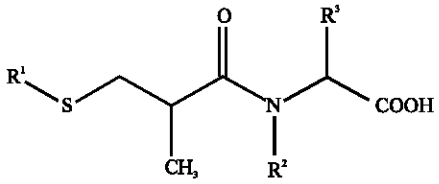
In conclusion, the validated QSAR models generated in the present study provide important information concerning the geometrical and structural requirements for the desired biological activity and can be used for the effective design of new, more potent angiotensin-converting enzyme inhibitors.

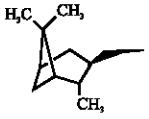
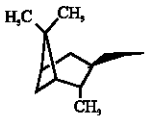
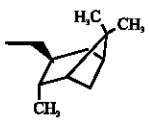
ACKNOWLEDGMENT

Computational resources were provided by Banasthali University and the authors thank the Vice Chancellor for extending all the necessary facilities.

APPENDIX

Table A1: Structure and biological activity data of ACE inhibitors used in QSAR analysis



Compound	R^1	R^2	R^3	IC_{50} (μm)	Log ($1/IC_{50}$)
12	H	H	H	0.210	0.6777
13	H	CH_3	H	0.130	0.8860
14	H	C_2H_5	H	0.075	1.1249
15	H	$(CH_3)_2CH$	H	0.072	1.1426
16	CH_3CO	$(CH_3)_2CH$	H	5.900	-0.7708
17	H	c-C_3H_5	H	0.030	1.5228
18	CH_3CO	c-C_3H_5	H	0.540	0.2676
19	H	c-C_3H_5	CH_3	0.079	1.1023
20	CH_3CO	c-C_3H_5	CH_3	0.220	0.6575
21	H	c-C_4H_7	H	0.018	1.7447
22	CH_3CO	c-C_4H_7	H	0.220	0.6575
23b	H	c-C_5H_9	H	0.016	1.7958
24	CH_3CO	c-C_5H_9	H	0.082	1.0861
25	H	c-C_6H_{11}	H	0.035	1.4559
26	CH_3CO	c-C_6H_{11}	H	0.270	0.5680
27	H	c-C_7H_{13}	H	0.031	1.5086
28	CH_3CO	c-C_7H_{13}	H	0.088	1.0555
29	H		H	0.032	1.4948
30	CH_3CO		H	0.020	1.6989
31	CH_3CO		H	0.052	1.2839
32	H		H	0.44	0.3565
33	CH_3CO		H	0.085	1.0705
34	H		H	0.16	0.7958

Tabel A1: Continued

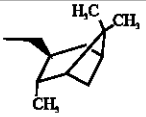
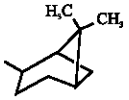
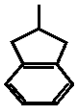
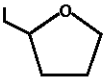
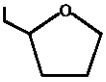
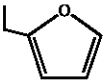
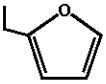
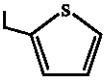
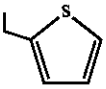
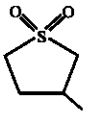
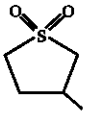
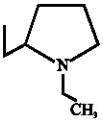
Compound	R^1	R^2	R^3	IC_{50} (μm)	Log ($1/IC_{50}$)
35	CH_3CO		H	0.14	0.8538
36	CH_3CO		H	0.045	1.3467
37	H		H	0.031	1.5086
38	CH_3CO		H	0.34	0.4685
39	H	$CH_3OCH_2CH_2$	H	0.095	1.0222
40	H	$CH_3S(CH_2)_3$	H	0.055	1.2596
41	CH_3CO	$CH_3S(CH_2)_3$	H	0.90	0.0457
42	H		H	0.13	0.886
43	CH_3CO		H	1.9	-0.2787
44	H		H	0.17	0.7695
45	CH_3CO		H	0.70	0.1549
46	H		H	0.055	1.2593
47	CH_3CO		H	0.75	0.1249
48	H		H	0.28	0.5528
49	CH_3CO		H	0.28	0.5528
50	H		H	0.64	0.1938
51	H	$CH{=}CHCH_2$	H	0.27	0.5686
52	CH_3CO	$CH{=}CHCH_2$	H	4.5	-0.6532
53	H	C_6H_5	H	0.30	0.5228
54	CH_3CO	C_6H_5	H	0.30	0.5228

Table A1: Continued

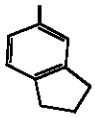
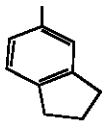
Compound	R^1	R^2	R^3	IC_{50} (μm)	Log ($1/IC_{50}$)
55	H	2-$(CH_3)C_6H_4$	H	0.120	0.9208
56	CH_3CO	2-$(CH_3)C_6H_4$	H	0.550	0.2596
57	H	3-$(CH_3)C_6H_4$	H	0.019	1.7212
58	CH_3CO	3-$(CH_3)C_6H_4$	H	0.075	1.1249
59	H	4-$(CH_3)C_6H_4$	H	0.005	2.3010
60	CH_3CO	4-$(CH_3)C_6H_4$	H	0.130	0.8860
61	H	3,5-$(CH_3)_2C_6H_3$	H	0.044	1.3565
62	CH_3CO	3,5-$(CH_3)_2C_6H_3$	H	0.044	1.3565
63	H		H	0.033	1.4814
64	CH_3CO		H	0.048	1.3187
65	CH_3CO	3-$(CH_3O)C_6H_4$	H	0.110	0.9586
66	CH_3CO	3-$(CH_3S)C_6H_4$	H	0.075	1.1249
67	CH_3CO	3-FC_6H_4	H	0.051	1.2924
68	H	4-FC_6H_4	H	0.023	1.6382
69	CH_3CO	4-FC_6H_4	H	0.600	0.2218
70	H	4-(*n*-$C_4H_9)C_6H_4$	H	0.190	0.7212
71	CH_3CO	4-(*n*-$C_4H_9)C_6H_4$	H	0.064	1.1938
72	CH_3CO	4-(*i*-$C_3H_7)C_6H_4$	H	0.060	1.2218
73	$(CH_3)_3CCH_2CO$	c-C_5H_9	H	15.000	-1.1760
74c (pivopril)	$(CH_3)_3CCO$	c-C_5H_9	H	3.600	-0.5563

Table A2: Actual activity, predicted activity and corresponding residuals for the training and test set of compounds

		Predicted activity		Residual value	
Compound	Actual activity log ($1/IC_{50}$)	MLR	PLS	MLR	PLS
Training set					
12	0.6777	0.40579	0.78670	0.27191	-0.109
13	0.8860	0.81416	0.89382	0.07184	-0.0078
15	1.1426	0.99781	0.95370	0.14479	0.1889
16	-0.7708	0.47385	0.41721	-1.24470	-1.1880
17	1.5228	1.18017	1.26149	0.34263	0.26132
19	1.1023	1.23113	1.31265	-0.12880	-0.2104
20	0.6575	0.82772	0.90333	-0.17020	-0.2458
21	1.7447	1.06562	1.08803	0.67908	0.65667
22	0.6575	0.61306	0.62943	0.04444	0.02807
23b	1.7958	1.32717	1.27147	0.46863	0.52433
24	1.0861	0.95117	0.88253	0.13493	0.20357
25	1.4559	1.30582	1.22211	0.15008	0.23379
26	0.5680	0.88620	0.79125	-0.31820	-0.2233
27	1.5086	1.22863	1.09402	0.27997	0.41458
28	1.0555	0.75771	0.61596	0.29779	0.43954
29	1.4948	1.53516	1.46713	-0.04040	0.02767

Table A2: Continued

		Predicted activity		Residual value	
Compound	Actual activity log ($1/IC_{50}$)	MLR	PLS	MLR	PLS
30	1.6989	1.19889	1.12528	0.50001	0.57362
31	1.2839	1.17226	1.10390	0.11164	0.18000
32	0.3565	1.15401	1.22526	-0.79750	-0.86880
34	0.7958	0.95310	1.03868	-0.15730	-0.24290
35	0.8538	1.13423	1.15924	-0.28040	-0.30540
37	1.5086	1.70102	1.61331	-0.19240	-0.10470
38	0.4685	1.40100	1.30125	-0.93250	-0.83280
39	1.0222	0.74435	0.79943	0.27785	0.22277
40	1.2596	0.48522	0.53759	0.77438	0.72201
41	0.0457	-0.04740	-0.00810	0.09312	0.05382
42	0.8860	0.76759	0.84209	0.11841	0.04391
43	-0.2787	0.29525	0.36026	-0.57400	-0.63900
44	0.7695	0.81198	0.88776	-0.04250	-0.11830
46	1.2593	0.96727	1.02753	0.29203	0.23178
47	0.1249	0.51566	0.56495	-0.39080	-0.44010
49	0.5528	0.40029	0.36439	0.15251	0.18841
50	0.1938	0.73530	0.80984	-0.54150	-0.61600
51	0.5686	0.71164	0.78821	-0.14300	-0.21960
53	0.5228	1.23370	1.28962	-0.71090	-0.76680
54	0.5228	0.80119	0.84729	-0.27840	-0.32450
55	0.9208	1.28401	1.31357	-0.36320	-0.39280
56	0.2596	0.89056	0.89330	-0.63100	-0.63370
57	1.7212	1.28967	1.31671	0.43153	0.40449
59	2.3010	1.31691	1.32292	0.98409	0.97808
60	0.8860	1.03443	0.98546	-0.14840	-0.09950
61	1.3565	1.32322	1.31857	0.03328	0.03793
62	1.3565	0.97512	0.94964	0.38138	0.40686
63	1.4814	1.59907	1.53751	-0.11770	-0.05610
65	0.9586	0.80549	0.79550	0.15312	0.16310
66	1.1249	0.92494	0.87633	0.19996	0.24857
67	1.2924	0.83304	0.87382	0.45936	0.41858
68	1.6382	1.27325	1.31640	0.36495	0.32180
70	0.7212	1.15057	1.15109	-0.42940	-0.42990
71	1.1938	0.99892	0.94051	0.19489	0.25329
72	1.2218	1.17258	0.84165	0.04922	0.38015
73	-1.1760	-1.39140	-1.44110	0.21538	0.26507
74c	-0.5563	-0.51620	-0.55860	-0.04010	0.00234
Test set					
14	1.1249	0.90990	1.00227	0.21500	0.12263
18	0.2676	0.87596	0.94392	-0.60836	-0.67632
33	1.0705	0.79220	0.86481	0.27830	0.20569
36	1.3467	1.60585	1.46628	-0.25915	-0.11958
45	0.1549	0.35028	0.44534	-0.19538	-0.29044
48	0.5528	0.87060	0.87608	-0.31780	-0.32328
52	-0.6532	0.15097	0.25864	-0.50223	-0.39456
58	1.1249	0.99442	0.98591	0.13048	0.13899
64	1.3187	1.37110	1.29074	-0.05240	0.02796
69	0.2218	0.89825	0.93197	-0.67645	-0.71017

Table A3: Assessment of the Lipinski's rule of five

Compound	ADME weight (whole molecule)	ADME H-bond acceptors (whole molecule)	ADME H-bond donors (whole molecule)	ADME log P (whole molecule)	ADME violations (whole molecule)
Training set					
12	177.24	3	3	-0.4697	0
13	191.27	3	2	-0.2232	0
15	219.33	3	2	0.5324	0
16	261.37	4	1	0.4182	0
17	217.31	3	2	0.1730	0
19	231.34	3	2	0.7105	0
20	273.38	4	1	0.5963	0
21	231.34	3	2	0.5963	0
22	273.38	4	1	0.4551	0
23b	245.37	3	2	0.9656	0
24	287.41	4	1	0.8514	0
25	259.40	3	2	1.3619	0
26	301.44	4	1	1.2477	0
27	273.43	3	2	1.7582	0
28	315.47	4	1	1.6440	0
29	271.41	3	2	1.1949	0
30	313.45	4	1	1.0807	0
31	313.45	4	1	1.0807	0
32	327.53	3	2	2.5305	0
34	327.53	3	2	2.5305	0
35	369.57	4	1	2.4163	0
37	293.41	3	2	1.8574	0
38	335.45	4	1	1.7432	0
39	235.33	4	2	-0.3880	0
40	265.42	3	2	0.1066	0
41	307.46	4	1	-0.0076	0
42	261.37	4	2	0.0082	0
43	303.41	5	1	-0.1060	0
44	258.34	4	2	0.2544	0
46	274.40	3	2	0.5977	0
47	316.44	4	1	0.4835	0
49	337.44	6	1	-0.0604	0
50	288.45	4	2	0.4946	0
51	215.29	3	2	0.0506	0
53	253.34	3	2	1.4585	0
54	295.38	4	1	1.3443	0
55	267.37	3	2	1.9257	0
56	309.41	4	1	1.8115	0
57	267.37	3	2	1.9257	0
59	267.37	3	2	1.9257	0
60	309.41	4	1	1.8115	0
61	281.40	3	2	2.3929	0
62	323.44	4	1	2.2787	0
63	293.41	3	2	2.2852	0
65	325.41	5	1	1.0916	0
66	341.47	4	1	1.4349	0

Table 3A: Continued

Compound	ADME weight (whole molecule)	ADME H-bond acceptors (whole molecule)	ADME H-bond donors (whole molecule)	ADME log P (whole molecule)	ADME violations (whole molecule)
67	313.37	4	1	1.4838	0
68	271.33	3	2	1.5980	0
70	309.46	3	2	3.1146	0
71	351.50	4	1	3.0004	0
72	337.47	4	1	2.5383	0
73	343.53	4	1	2.6396	0
74c	329.50	4	1	2.7071	0
Test set					
14	205.30	3	2	0.1193	0
18	259.37	4	1	0.0588	0
33	369.57	4	1	2.4163	0
36	341.51	4	1	1.8444	0
45	300.38	5	1	0.1402	0
48	295.40	5	2	-0.9462	0
52	257.33	4	1	-0.0636	0
58	309.41	4	1	1.8115	0
64	335.45	4	1	2.1710	0
69	313.37	4	1	1.4838	0

REFERENCES

Abhilash, T., M. Thakur and S. Thakur, 2006. QSAR study on triazine derivatives as DHFR inhibitors using electrotopological state. Asian J. Biochem., 1: 138-147.

Bajorath, J., 2005. Molecular Similarity Methods and Quantitative Structure-Activity Relationship Models as Tools for Virtual Screening. In: Drug Discovery Handbook, Gad, S.C. (Ed.). Wiley Interscience, New Jersey, pp: 87-122.

Bersuker, I.B., S. Bahcüeci and J.E. Boggs, 2000. Improved electron-conformational method of pharmacophore identification and bioactivity prediction. Application to angiotensin converting enzyme inhibitors. J. Chem. Inform. Comput. Sci., 40: 1363-1376.

Bohacek, R., S. De Lombaert, C. McMartin, J. Priestle and M. Grütter, 1996. Three-dimensional models of ACE and NEP inhibitors and their use in the design of potent dual ACE/NEP inhibitors. J. Am. Chem. Soc., 118: 8231-8249.

DePriest, S.A., D. Mayer, C.B. Naylor and G.R. Marshall, 1993. 3D-QSAR of angiotensin-converting enzyme and thermolysin inhibitors: A comparison of CoMFA models based on deduced and experimentally determined active site geometries. J. Am. Chem. Soc., 115: 5372-5384.

Fogo, A.B., 1999. New insights into the renin angiotensin system and hypertensive renal disease. Curr. Hypertens. Rep., 1: 187-194.

Golbraikh, A., D. Bonchev and A. Tropsha, 2001. Novel chirality descriptors derived from molecular topology. J. Chem. Inform. Comput. Sci., 41: 147-158.

Gupta, S.P. and S. Kumaran, 2006. Quantitative structure-activity relationship studies on benzodiazepine hydroxamic acid inhibitors of matrix metalloproteinases and tumor necrosis factor-α converting enzyme. Asian J. Biochem., 1: 47-56.

Hansch, C. and T. Fujita, 1964. p-δ-π analysis, a method for the correlation of biological activity and chemical structure. J. Am. Chem. Soc., 86: 1616-1626.

Hoffman, B., S.J. Cho, W. Zheng, S. Wyrick, D.E. Nichols, R.B. Mailman and A. Tropsha, 1999. Quantitative structure-activity relationship modeling of dopamine D1 antagonists using comparative molecular field analysis, genetic algorithms-partial least-squares and K nearest neighbor methods. J. Med. Chem., 42: 3217-3226.

Jackson, E.K., 2001. Renin and Angiotensin. In: Goodman and Gilman's the Pharmacologic Basis of Therapeutics, Hardman, J.G., L.E. Limberd and A.G. Gilman (Eds.). 10th Edn., McGraw-Hill, New York, pp: 809-829.

Jain, A. and S.C. Chaturvedi, 2008. Rationalization of physicochemical property of some substituted benzimidazole bearing acidic heterocyclic towards angiotensin II antagonist: A QSAR approach. Asian J. Biochem., 3: 330-336.

Jamloki, A., C. Karthikeyan, S.K. Sharma, N.S.H.N. Moorthy and P. Trivedi, 2006. QSAR studies on some GSK-3α Inhibitory 6-aryl-pyrazolo (3,4-b) pyridines. Asian J. Biochem., 1: 236-243.

Karthikeyan, C., P.M. Kumar, N.S.H.N. Moorthy, S.K. Shrivastava and T. Piyush, 2006. Quantitative structure activity relationships of some selective inhibitors of glucagon receptor: A hansch approach. Asian J. Biochem., 1: 307-315.

Karthikeyan, C., D. Santosh, N.S.H.N. Moorthy and P. Trivedi, 2007. QSAR analysis of HIV-1 reverse transcriptase inhibitory 5-Alkyl-2-[(Aryl and Alkyloxylcarbonylmethyl) Thio]-6-(1-Napthylmethyl) Pyrimidin-4 (3H)-Ones. Int. J. Virol., 3: 19-27.

Kier, L.B. and L.H. Hall, 1999. The Kappa Indices for Modeling Molecular Shape and Flexibility. In: Topological Indices and Related Descriptors in QSAR and QSPR, Devillers, J. and A.T. Balaban (Eds.). Gordon and Breach Science Publishers, The Netherlands, pp: 455-489.

Klocker, J., B. Wailzer, G. Buchbauer and P. Wolschann, 2002. Bayesian neural networks for aroma classification. J. Chem. Inf. Comput. Sci., 42: 1443-1449.

Kovatcheva, A., G. Buchbauer, A. Golbraikh and P. Wolschann, 2003. QSAR modeling of alpha campholenic derivatives with sandalwood odor. J. Chem. Inform. Comput. Sci., 43: 259-266.

Kubinyi, H., 1996. Evolutionary variable selection in regression and PLS analyses. J. Chemometr., 10: 119-133.

Kumar, R., R. Sharma, K. Bairwa, R.K. Roy, A. Kumar and A. Baruwa, 2010. Modern development in ACE inhibitors. Der Pharmacia Lett., 2: 388-419.

Kuoppala, A., K.A. Lindstedt, J. Saarinen, P.T. Kovanen and J.O. Kokkonen, 2000. Inactivation of bradykinin by angiotensin-converting enzyme and by carboxypeptidase N in human plasma. Am. J. Physiol. Heart. Circ. Physiol., 278: H1069-H1074.

Latini, R., A.P. Maggioni, M. Flather, P. Sleight and G. Tognoni, 1995. ACE inhibitor use in patients with myocardial infarction. Summary of evidence from clinical trials. Circulation, 92: 3132-3137.

Liao, C., A. Xie, L. Shi, J. Zhou and X. Lu, 2004. Eigenvalue analysis of peroxisome proliferator-activated receptor gamma agonists. J. Chem. Inf. Comput. Sci., 44: 230-238.

Lipinski, C.A., F. Lombardo, B.W. Dominy and P.J. Feeney, 1997. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev., 23: 3-25.

Mayer, D., C.B. Naylor, I. Motoc and G.R. Marshall, 1987. A unique geometry of the active site of angiotensin-converting enzyme consistent with structure-activity studies. J. Comput.-Aided Mol. Des., 1: 3-16.

Moorthy, N.S.H.N. and P. Trivedi, 2006. QSAR modeling of some 2-methoxy Acridones: Cytotoxic agents in multi drug resistant cells. Int. J. Cancer Res., 2: 267-276.

Nesto, R.W. and S. Zarich, 1998. Acute myocardial infarction in diabetes mellitus: Lessons learned from ACE inhibition. Circulation, 97: 12-15.

Paliwal, S., A. Narayan and S. Paliwal, 2009. Quantitative structure activity relationship analysis of dicationic diphenylisoxazole as potent anti-trypanosomal agents. QSAR Comb. Sci., 28: 1367-1375.

Paliwal, S.K., M. Pal and A.A. Siddiqui, 2010. Quantitative structure activity relationship analysis of angiotensin II AT1 receptor antagonists. Med. Chem. Res., 19: 475-489.

Panday, S.K., M. Dikshit and D.K. Dikshit, 2009. Synthesis of N-[3'-(acetylthio)alkanoyl] and N-[3'-mercaptoalkanoyl]-4-α(s)-(phenylmethyl) pyroglutamic acids and prolines as potent ACE inhibitors. Med. Chem. Res., 18: 566-578.

Rogers, D. and A.J. Hopfinger, 1994. Application of genetic function approximation to quantitative structure-activity relationships and quantitative structure-property relationships. J. Chem. Inf. Comput. Sci., 34: 854-866.

Sadowski, J. and J. Gasteiger, 1993. From atoms and bonds to three-dimensional atomic coordinates: Automatic model builders. Chem. Rev., 93: 2567-2581.

San Juan, A.A. and S.J. Cho, 2005. 3D-QSAR studies on angiotensin-converting enzyme (ACE) inhibitors: A molecular design in hypertensive agents. Bull. Korean Chem. Soc., 26: 952-958.

Shen, M., A. LeTiran, Y. Xiao, A. Golbraikh, H. Kohn and A. Tropsha, 2002. Quantitative structure-activity relationship analysis of functionalized amino acid anticonvulsant agents using k nearest neighbor and simulated annealing PLS methods. J. Med. Chem., 45: 2811-2823.

Shreedharan, R. and D. Bockenhauer, 2005. Congenital nephrotic syndrome responsive to angiotensin-converting enzyme inhibition. Pediatr. Nephrol., 20: 1340-1342.

Suh, J.T., J.W. Skiles, B.E. Williams, R.D. Youssefyeh and H. Jones *et al*., 1985. Angiotensin-converting enzyme inhibitors. New orally active antihypertensive (mercaptoalkanoyl)- and [(acylthio)alkanoyl]glycine derivatives. J. Med. Chem., 28: 57-66.

Sutters, M., 2008. Systemic Hypertension. In: Current Medical Diagnosis and Treatment, McPhee, S.J., M.A. Papadakis and L.M. Tierney (Eds.). McGraw-Hill, New Jersey, pp: 371-399.

Thakur, A., B.K. Tiwari, M. Thakur, S. Thakur, N.D. Pandey and S.S. Narvi, 2007. 2D, 3D modeling of inhibition activity of reverse transcriptase-1 by HEPT derivatives. Asian J. Biochem., 2: 84-100.

Tropsha, A., S.J. Cho and W. Zheng, 1999. New Tricks for an Old Dog: Development and Application of Novel QSAR Methods for Rational Design of Combinatorial Chemical Libraries and Database Mining. In: Rational Drug Design: Novel Methodology and Practical Applications, Parril, A.L. and M.R. Reddy (Eds.). ACS Symposium Series 719, American Chemical Society, Washington DC., pp: 198-211.

Vengurlekar, S., R. Sharma and P. Trivedi, 2010. Two- and three-dimensional QSAR studies on benzyl amide-ketoacid inhibitors of HIV integrase and their reduced analogues. Med. Chem. Res., 19: 1106-1120.

Verloop, A., 1961. The STERIMOL Approach to Drug Design. Marcel Dekker, New York.

Vinter, J.G., A. Davis and M.R. Saunders, 1987. Strategic approaches to drug design. I. An integrated software framework for molecular modelling. J. Comput. Aided Mol. Des., 1: 31-51.

Wiener, H., 1947. Structural determination of paraffin boiling points. J. Am. Chem. Soc., 69: 17-20.

Wright, J.W., S. Mizutani and J.W. Harding, 2008. Pathways involved in the transition from hypertension to hypertrophy to heart failure. Treatment strategies. Heart Fail. Rev., 13: 367-375.

Wyvratt, M.J. and A.A. Patchett, 1985. Recent developments in the design of angiotensin-converting enzyme inhibitors. Med. Res. Rev., 5: 483-531.

Yokoyama, H., O. Tomonaga, M. Hirayama, A. Ishii and M. Takeda *et al.*, 1997. Predictors of the progression of diabetic nephropathy and the beneficial effect of angiotensin-converting enzyme inhibitors in NIDDM patients. Diabetologia, 40: 405-411.

Zheng, W. and A. Tropsha, 2000. A novel variable selection quantitative structure-property relationship approach based on the k-nearest-neighbor principle. J. Chem. Inform. Comput. Sci., 40: 185-194.