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2D-and 3D-Qsar Studies of Substituted 4h-Pyrido [1, 2-a] Pyrimidin-4-Ones Angiotensin II Receptor Antagonists

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Abstract: Quantitative Structure-Activity Relationships (QSAR) analyses have been attempted on a Substituted 4H-pyrido [l, 2-a] pyrimidin-4-ones derivatives using MLR model of Hansch to explain the structural requirements of derivatives for Angiotensin II Receptor Antagonists .Out of various descriptors studied, torsion energy, *Vdw, log P* showed good correlation with Angiotensin II Receptor Antagonists activity (Pred_r^2= 0.8217, q^2 = 0.7136) k-Nearest Neighbor Molecular Field Analysis (kNN-MFA) method combined with various selection procedures. By using kNN-MFA approach, various 3D QSAR models were generated to study the effect of steric and electrostatic descriptors on anti-hypertensive activity. The model with good external and internal predictivity for the training and test set has shown cross validation (q^2) and external validation (pred_r^2) values of = 0.6705 and 0.7642, respectively. QSAR model was to design and predict accurately the modeled properties of the newly synthesized compounds as antihypertensive.

Key words: Angiotensin II (Ang II) · 2D QSAR · KNNMFA · Antihypertensive

INTRODUCTION

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure through the actions of angiotensin II (Ang II) (vasoconstriction, aldosterone secretion, renal sodium reabsorption and nor epinephrine release) and thus is an appropriate target for therapeutic intervention in hypertension. The renin-angiotensin system (RAS) plays a key role in regulating cardiovascular homeostasis and electrolyte/ fluid balance in normotensive and hypertensive subjects [1]. The octapeptide angiotensin II (Ang II) is produced by the rennin angiotensin system (RAS) and is a potent vasoconstrictor and thus plays an important role in the pathophysiology of hypertension [2]. Angiotensin II plays a key role in the regulation of cardiovascular homeostasis. Acting on both the "content"and the "container", Ang II regulates blood volume and vascular resistance. The wide spectrum of Ang II target tissues includes the adrenals, kidney, brain, pituitary gland, vascular smooth muscle and the sympathetic nervous system. Angiotensin is not only a blood borne hormone that is produced and acts in the circulation but is also formed in many tissues such as brain, kidney, heart and blood vessels. This has led to the suggestion that Ang II may also function as a paracrine and autocrine hormone, which induces cell growth and proliferation and controls extracellular matrix formation [3-5]. Quantitative structure activity relationship (QSAR) is one of the major tools in drug discovery to explore ligand-receptor/enzyme interactions, especially when either the structural details of the target are not known or protein binding data of ligand is unavailable [6]. Since, there is a need to design new Ang II receptor, it was thought worthwhile to study the Quantitative Structure -Activity Relationship (QSAR) of existing dual active molecules. This would allow the identification of a common set of chemical properties/structural requirements that affects both activities. Additionally, it would provide a better understanding and a common handle to design new potent dual active molecules. For the purpose of developing a dual-response model, multiple regression method was chosen in the present study. Multiple regressions are a statistical method which correlates a set of dependent variables (activities) with a set of independent variables (molecular descriptors). Structural variations in the molecular fields of particular regions in the space can be studied and QSAR models can be used

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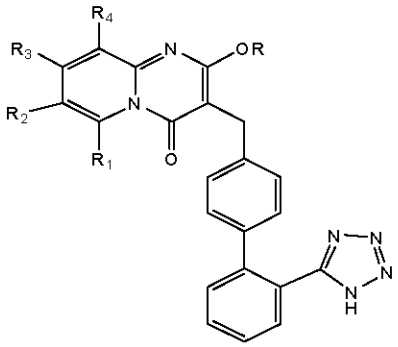
to give an insight in the design of potent antihypertensive agents. Newly reported method k-Nearest Neighbor Molecular Field Analysis (k-NN MFA) adopts a k-Nearest Neighbor principle for generating relationship of molecular fields with the experimentally reported activity. This method utilizes the active analogue principle that lies at the foundation of medicinal chemistry [7]. A number of quantitative structure-activity relationship (QSAR) studies related to design of angiotensin II receptor antagonists drugs have also been reported [8-12]. No molecular modelling QSAR studies have been done till date on this class of compounds, so we attempt to subject this new class of compounds for an effective QSAR analysis.

MATERIALS AND METHODS

The Ang II receptor antagonistic activities of Substituted 4H-pyrido [l, 2-a] pyrimidin-4-ones are listed in Table 1. A dataset of twelve molecules have been taken from literature [13]. The biological activity values [IC_{50} (μM)] reported in micro molar units were converted to their molar units and then further to negative logarithmic scale and subsequently used as the dependent variable for the QSAR analysis. All biological activities used in present study were expressed as: pIC50=-log10 IC_{50}, where IC_{50} is the micro molar concentration of the inhibitor producing 50% inhibition. The conversion was done in order to linearly relate free energy of the interaction of compounds with receptor and to reduce the skewness of the data set. The total set of compounds was (12 compounds) for generating 2D QSAR models and a test set for validating the quality of the models. Selection of the training set and test set molecules was done on the basis of structural diversity and a wide range of activity such that the test-set molecules represent a range of biological activity similar to that of the training set; thus, the test set is truly representative of the training set. Molecular Modelling studies and Quantum mechanical calculations were performed using CS ChemOffice [14] Software version 6.0 (Cambridge software) running on a IV processor. All molecules were built using Chemdraw Ultra 6.0 and subjected to energy minimization using Allinger's MM2 force field. The minimization is continued until the root mean square (RMS) gradient value reaches a value smaller than 0.1 kcal/mol Å. The Hamiltonian approximations Austin model-1 method. The sketched 2D structures were converted to 3D structures and were subjected to energy minimized using semi-empirical quantum mechanics module implemented on molecular orbital package (MOPAC) version, fixing maximum iteration limit to 1000, root mean square (RMS) gradient to 0.001 kcal/mol and applying the theory of AM-1 Hamiltonian using closed shell restricted wave function.

Table 1: Structures of Substituted 4H-pyrido [l, 2-a] pyrimidin-4-ones



Comp	R_1	R_2	R_3	R_4	R	IC 50	pIC50
7a	H	H	H	H	$-CH_3$	1.4	5.853
7b*	H	H	H	H	$-CH_2$ CH_3	4.4	5.356
7c	H	$CH(OH)CH_3$	H	H	$-CH_2CH(CH_3)_2$	1.0	6.00
7d	H	H	H	$-CH_3$	$-CH_2CH_2CH_3$	6	5.221
7e*	H	$-CH_3$	H	H	$-CH(CH_3)_2$	6	5.221
7f	H	$-COOC_2H_5$	H	H	$-CH(CH_3)_2$	4.9	5.309
7g	H	-COOH	H	H	$-CH(CH_3)_2$	69.3	4.159
7h*	H	$-CH_3$	H	H	$-CH_2CH(CH_3)_2$	4	5.397
7i	H	- CH_3	H	H	$-CH_2$ CH_2CH_3	1.6	5.795
7j	H	H	- CH_3	H	$-CH_2$ CH_2CH_3	4	5.397
7k	H	H	H	H	$-CH_2$ $(CH_2)_2CH_3$	2.4	5.619
7l	H	H	H	H	$-CH_2$ CH_2CH_3	0.25	6.602

*test compound

In order to cover wide range of physiochemical properties to describe the observed activity in a better way, thermodynamic, electronic and steric parameters were calculated for the energy minimized and geometrically optimized structures from MM2 server. The physicochemical properties calculated include thermodynamic, steric and electronic descriptors. Molar refractivity, torsion energy (TOE), stretch bend energy (SBE), logP and bend energy (BE) are descriptors of thermodynamic property. The steric descriptors calculated were Connolly accessible area (CAA), Connolly molecular area (CMA), Connolly solvent excluded volume (CSEV), molecular weight, principal moments of inertia-*x* component (PMI-X), principal moments of inertia-*y* component (PMI-Y), principal moments of inertia-*z* component (PMI-Z) and Ovality. Electronic descriptors such as dipole moment (DM), electronic energy (EE), highest occupied molecular orbital energy (HOMO), lowest unoccupied molecular orbital energy (LUMO), repulsion energy (RE) and total energy (TE) were also calculated. The topological descriptors calculated were Balaban index (BI), cluster count (CC), diameter (D), molecular topological index (MTI), radius (R), shape attributes (SA), shape coefficient (SC), sum of degree (SOD), sum of valence degree (SOVD), sum of total connectivity (TC), total valence connectivity (TVC) and the Wiener index (WI). The relationship between response variable (as a dependent variable) and various physicochemical as well as structural descriptors (as independent variables) were established by step-wise linear multiple regression analysis using VALSTAT [15] running on a Pentium 4 processor (CPU 3.00 GHz HT). Significant descriptors were chosen on the basis of statistical data of analysis. The program employs a stepwise technique, *i.e.* only one parameter at a time was added to a model and always in the order of most significant to least significant in terms of F-test values. Statistical parameters were calculated subsequently for each step in the process, so the significance of the added parameter could be verified. The goodness of the correlation is tested by the regression coefficient (R^2), the F-test and the standard error of estimate (SEE). The t-test and the level of significance of each coefficient, as well as the confidence limits of the regression coefficient, are also reported. The squared correlation coefficient (or coefficient of multiple determination), R^2, is a measure of the fit of the regression model. Correspondingly, it represents the part of the variation in the observed (experimental) data that is explained by the model. The correlation coefficient values closer to 1.0 represent the better fit of the model. The F-test reflects the ratio of the variance explained by the model and the variance due to the error in the model (i.e. the variance not explained by the model). High values of the F-test indicate that the model is statistically significant. The standard error is measured by the error mean square, s^2, which expresses the variation of the residuals or the variation about the regression line. Thus, the standard error measures the model error. If the model is correct, it is an estimate of the error of the data variance. The t-test measures the statistical significance of the regression coefficients. The higher t-test values correspond to the relatively more significant regression coefficients. The model, which passed the statistical diagnosis with as few descriptors as possible was chosen. When adding of another descriptor in stepwise addition did not improve significantly the statistics of a model, it was determined that the optimum subset of descriptor for QSARs had been achieved. Besides deriving quantitative models of statistical significance, an important aspect of QSAR modeling is validating the model since a good statistical fit does not guarantee the predictive ability of the model. In view of above, the internal consistency of the selected models was assessed by cross-validation method following a leave-one-out scheme using the in-house program VALSTAT. In this method, one data point is systematically deleted from the dataset and a QSAR model is constructed on the basis of reduced dataset and the model is subsequently used to predict the removed data point. The procedure was repeated until a completed set of predicted values is generated. The validation parameters calculated are squared cross-correlation coefficient (Q2), standard deviation of sum of square of difference between predicted and observed values (SPRESS) and standard deviation of error of prediction (SDEP). Q2 values greater than five and low SPRESS and SDEP values (<0.5) can be considered as a proof of the high predictive ability of the QSAR models. Finally, the derived QSAR models were used for the prediction of the activity values of the compounds in the test set and the external validation parameter, predictive r^2 (r^2pred) was calculated for evaluating the predictive capacity of the model. A value of r^2pred greater than 3 indicate the good predictive capacity of the QSAR model. Multiple linear regression analysis and other statistical analysis were carried out on all the 12 molecules. The outlier molecules were then removed to improve the equation's predictive power. The final set of equations was obtained using 12 molecules and the best equation was obtained by using the optimal combination of descriptors. Descriptors were

selected for the final equation based on their correlation coefficients and those descriptors having inter-correlation coefficient below 0.7 were considered, to select the best equation. Correlation matrix was obtained to justify the use of more than one variable in the study. The variables used were with maximum correlation to activity and minimum inter-correlation with each other. From the statistical viewpoint, the ratio of the number of samples (N) to the number of variables used (M) should not be very low; usually it is recommended that N/M=5. The statistical quality of the equations was judged by the parameters like correlation coefficient (r), explained variance (r^2), standard error of estimate(s) and the variance ratio or overall significance value (F).The accepted equations are validated for stability and predictive ability using "leave -one-out" and cross validation technique. The statistical parameters used to access the quality of the models are the predictive sum of squares (PRESS) of validation. Finally, the standard cross-validation correlation coefficient r^2 and q^2 are also calculated.

$$PRESS = \Sigma (Ypred - Y\ obs)^2$$

$$S_{press} = \sqrt{PRESS/ (n-k-1)}$$

n=no. of compounds used for cross-validation, yi= experimental value of the physic-chemical property for the i^{th} sample, y= value predicted by the model built without the sample i

3D-QSAR Studies and Alignment: The 3D QSAR computations were carried out on a VLife QSAR plus 3.5 [16] molecular modeling software. The 3D structures of the training and the test set of compounds were constructed using the Draw Molecule function in VLife QSAR Plus 3.5. Energy minimizations were performed for individual molecules as well as for the entire batch using the MMFF94 force field [17] and Gasteiger-Marsili charges[18] followed by AM-1 (Austin Model-1) Hamiltonian method available with the software with the convergence criterion of 0.001 kcal/mol A°. The position of each atom is important for kNN-MFA study because the descriptors calculation is based on the 3D-space grid. Thus, the method to determine the conformation of each molecule and the way to align molecules together are two sensitive input parameters to build a reasonable model. The template used for alignment of the most potent molecule (compound 7) was chosen as a reference molecule (Fig. 1a) to fit the training and test set of compounds by using the align molecules function

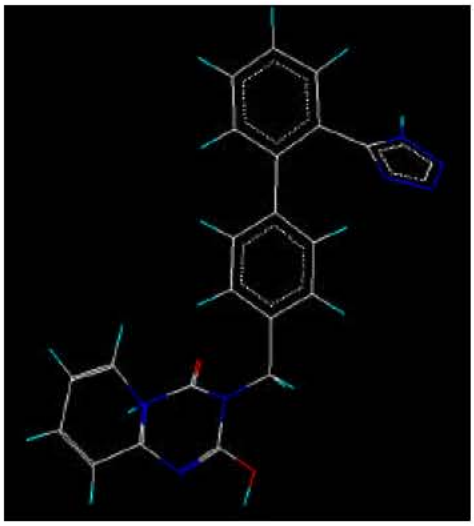


Fig. 1(a): Template-used alignment of molecules

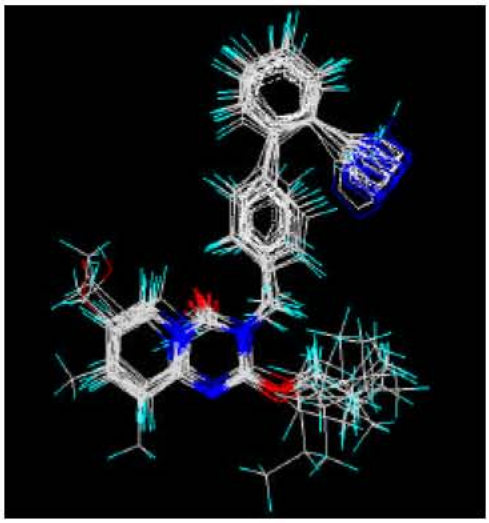


Fig. 1(b): Template-based alignment of molecules

available in the software. The resulting template based alignment model is shown in (Fig. 1b). The ensuing alignment model was subjected to kNN-MFA 3D QSAR studies.

kNN-MFA method: The kNN methodology relies on a simple distance learning approach whereby an unknown member is classified according to the majority of its k-nearest neighbors in the training set. The nearness is measured by an appropriate distance metric (e.g. a molecular similarity measure calculated using field interactions of molecular structures). The standard kNN method is implemented simply as follows: Calculate distances between an unknown object (u) and

all the objects in the training set; select k objects from the training set most similar to object u, according to the calculated distances; and classify object u with the group to which the majority of the k objects belongs. An optimal k value is selected by optimization through the classification of a test set of samples or by leave-one out cross-validation. In the present kNN-MFA study, (-17.4387 to15.8765) × (-15.3154 to12.3663) × (-10.6321 to 8.4097) A^0grid at the interval of 2.00 was generated around the aligned compounds. These interaction energy values are considered for relationship generation and utilized as descriptors to decide nearness between molecules. The QSAR models were developed using forward-backward variable selection method with pIC_{50}activity field as dependent variable and physico-chemical descriptors as independent variable having cross-correlation limit of 1, 0.8 and 0.9 for mode 1, model 2 and model 3 respectively. Selection of test and training set was done by sphere exclusion method having dissimilarity value of 8.0, for mode 1, model 2 and model 3 respectively.To derive the kNN-MFA descriptor fields, a 3D cubic lattice with grid spacing of 2 A° in x, y and z dimensions was created to encompass the aligned molecules. kNNMFA descriptors were calculated using an sp3 carbon probe atom with a van der Waals radius of 1.52 A° and a charge of +1.0 with default cut-off energy 30 kcal/mol and 10 kcal/mol to generate steric field energies, electrostatic and hydrophobic fields. The steric electrostatic and hydrophobic fields values were truncated at a default value of ±30 kcal/mol. A stereo view of the superimposed complexes based on alignment is shown in Fig. 1b. The regression analysis of kNN field was performed using distance-based weighted average and the predictive value of the model was evaluated by standard leave-one out (LOO) cross validation[20]. The cross-validated correlation coefficient served as a measure of the quality of the model. To test the utility of the model as a predictive tool, an external set of compounds with known activities (the test set) were used. The predictive r^2 calculation was based on molecules in the test set and was used to evaluate the predictive power of the kNN-MFA model.Simulated annealing (SA) is the simulation of a physical process, 'annealing', which involves heating the system to a high temperature and then gradually cooling it down to a preset temperature (e.g. room temperature). During this process, the system samples possible configurations distributed according to the Boltzmann distribution so that at equilibrium, low energy states are the most populated.

RESULTS AND DISCUSSION

In the present study we tried to develop with help chem.-office and 3D QSAR studies done by Vlife MDS 3.5, best QSAR model to explain the correlations between the physicochemical parameters and antihypertensive activities of Substituted 4H-pyrido [l, 2-a] pyrimidin-4-ones. Among several QSAR equations the best QSAR models were selected on the basis of various statistical parameters such as correlation coefficient ($R > 0.7$), squared correlation coefficient ($R^2 > 0.6$), standard error of estimate ($SEE < 0.3$) and F-test values at 99% significance level. Only those descriptors having inter-correlation coefficient below 0.7 were considered for the present study. The generated best models were validated for predictive ability inside the model (Leave One Out method) and outside the model (test and training set). . This method utilizes the active analogue principle that lies at the foundation of medicinal chemistry [21-23].

$$\text{Log } IC_{50} = 4.2176\ (\pm 0.4379) - 0.2165\ (\pm 0.1256)\ \mathit{Vdw} + 0.5497\ (\pm 0.3265)\ \mathit{log\ P} + 1.3426\ (\pm 1.7643)\ \text{TOE} + 0.8363\ (\pm 0.0046)\ \text{SOVD}$$

n=12, r=0.8952, r^2=0.8121, $q2$= 0.7136, std. =0.3698, Pred_r^2= 0.8217, F=79.8125, SEE = 0.1823, Spress = 0.4386, SDEP = 0.3287, R^2_{cv} = 0.2275

The model has a correlation coefficient of 0.8121 with 81.21 % explained variance in the Ang II activity. F statistics indicate statistical significance at 99% level as the calculated F value exceeds the tabulated F value, which is F (2, 43) = 79.8125. Since p-value from analysis of variance (ANOVA) table is less than 0.01, there exists statistically significant relationship between the descriptors Vdw and SOVD and biological activity. TOE and SOVD respectively exceed the critical value, making the model reliable. R respectively exceeds the critical value, making the model reliable. The model also exhibits good predictivity as established by the cross validation of the model. The model also good predictivity as established by the cross validation of the model. Predicted activity values were calculated using the correlation developed and a comparison was made with the observed values (Table 2). The contribution of topological descriptors SOVD and radius (R) revealed that topology of the molecules play important role in antihypertensive activity. SOVD shows positively contribution whereas radius negatively contributes to

Table 2: Observed and predicted activities of statistically significant models

Comp	pIC50	2D Predict Model-1	2D Predict Model-2	3D Predict Model-1	3D Predict Model-2
7a	5.853	5.39253	5.29402	5.45765	5.30334
7b	5.356	5.61868	5.49963	5.31993	5.77466
7c	6.000	5.63957	5.36113	5.81448	5.23252
7d	5.221	5.19787	5.32571	5.25908	5.30235
7e	5.221	4.92443	5.31432	5.30771	5.1027
7f	5.309	4.92678	5.0591	5.16234	5.99852
7g	4.159	4.32063	4.35573	4.24519	4.04317
7h	5.397	5.55649	5.30395	5.77634	4.97481
7i	5.795	5.47503	5.95589	5.98569	5.30344
7j	5.397	5.1864	5.117	5.01598	5.51854
7k	5.619	5.39253	5.13634	5.09472	5.11975
7l	6.602	6.31868	6.29402	6.21812	6.30334

biological activity. Radius (R) is defined as the smallest vertex eccentricity. The positive contribution of SOVD illustrates that increase in branching and presence of atoms is favorable for antihypertensive activity. The Van der waals energy is a thermodynamic parameter which can be defined as the sum of pair wise Vander waals interaction energy terms for atoms separated related to the structure of the molecule itself. VDW is Vander Waal's energy and contribute positively that is increasing in VDW cause increased antihypertensive activity.

$$\text{Log } IC_{50} = 2.5432\ (\pm 0.3218)\ \text{VDWE} - 1.0831\ (\pm 2.5472)\ \text{OVA} + 1.6905\ (\pm 0.2156)\ \text{DDE} + 0.6543\ (\pm 0.1654)\ \text{CAA}$$

n=12, r=0.8376, r^2=0.7965, *q*2= 0.6275, Pred_r^2= 0.7652, std. =0.1837, F=54.2187, SEE = 0.3276, Spress = 0.2165, SDEP = 0.6543, R^2_{cv} = 0.4376

Model 2 has good correlation between biological activity and parameters as *R* = 0.7965 and explains 79.65 % variance in Ang II activity. Low standard deviation of the model demonstrates accuracy of the model. The model showed overall significance level better than 99%, with the F(4,32,) = 54.2187 against values of 99% significance. Value of chance is less than 0.01, which shows there is significant relationship between Connolly accessible area (CAA) Van der waals energy (VDWE) Dipole-dipole Energy (DDE) and biological activity. Validation parameters bootstrapping r^2, r^2bs = 0.4398 and cross validated *r*2 (*q*2 = 0. 6275) reflects the good predictive power of the model. Connolly's solvent accessible area, a steric descriptor, represents the surface area that is in contact with the solvent. The descriptor bears negative coefficient in the model, suggesting increase in the bulkiness of the substituents and molecular solvent accessible surface area is not conducive to the activity. The descriptor Ovality in the second model bears a negative coefficient thereby it represent the steric hindrance associated with the bulk of the substituents. The descriptor DDE in the models represents the sum of electrostatic terms resulting from the interaction of two dipoles. The descriptor bears a positive coefficient, which suggests significance of dipole-dipole interactions for the Ang II activity of pyrimidin-4-ones. The observation possibly highlights ð- ð stacking interactions between the planar aromatic rings of the 4H-pyrido [l, 2-a] pyrimidin-4-ones moiety.

$$\text{Log } IC_{50} = 0.7683\ (\pm 0.2154)\ -0.0321\ (\pm 0.0845)\ \text{HOMO} + (\pm 0.1654)\ \text{DPL}$$

n=12, r=0.7842, r^2=0.7216, *q*2= 0.6432, std. =0.4371, Pred_r^2= 0.7132,F=28.542, SEE = 0.3265, Spress = 0.8754, SDEP = 0.2174, R^2_{cv} = 0.5832

Model 3 is a biparametric equation modelled for Ang II activity of compounds having H group at R_1 in Table 1. Compound was omitted since it is the only compound which has an N-substituent at R_1 on the aryl ring, whereas all other 12 compounds selected for model building have NH as the substituent. Compound 4 has a CH (OH) CH_3 atom at R_2 position. Its outlying behaviour may be due to favourable orientation of the polar atom at the R3 position towards the hydrophobic -$CH_2CH\ (CH_3)_2$ residues at the active site. This model gave insight into the nature of enzyme inhibition. The positive contribution of the highest occupied molecular orbital (HOMO) energy suggests favorable electron-donating groups in the aryl rings of the compound. The negative value of shape coefficient shows that the bulkier groups provide steric hindrance to drug-receptor binding and, hence, influence biological activity.DPL contributed positively to

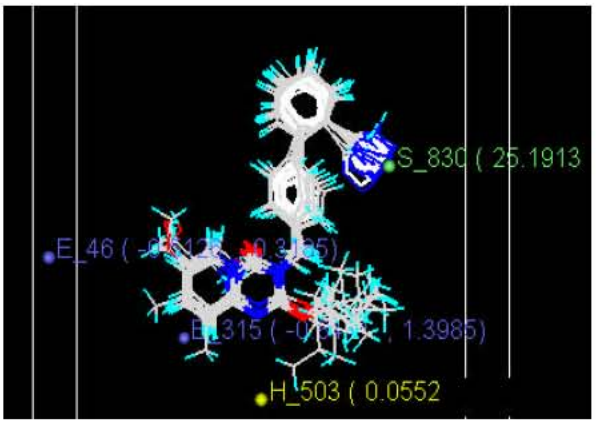


Fig. 1(c): Contour plots of models obtained by the SW-kNN-MFA method

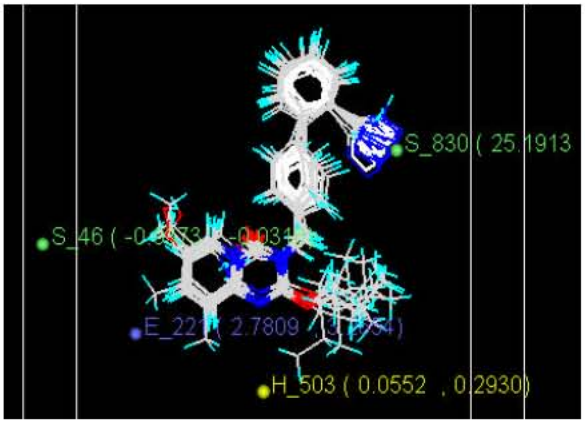


Fig. 1(d): Contour plots of models obtained by the SA-kNN-MFA method

the activity up to a small extent as suggesting that the moiety, which increases the charge distribution over the molecules, is favorable for the activity. It could be concluded that new molecules should be designed by considering the shape and size of the molecule, possessing at least one electron-withdrawing group on pyrimidin-4-ones moiety ring system and optimizing the hydrophobicity and bulkiness at R_1 position.

Model-4 Stepwise (SW) Variable Selection: pIC_{50}= 2.8754 +25.1913 (S_830) -0.5126 (E_46) -0.8441 (E_315) +0.0552 (H_503) + 1.5439

$N_{training}$ = 9, N_{test} = 3, Optimum Components = 4, DF = 24, r^2 = 0.8364, q^2 = 0.6705, F test = 51.326, r^2_se = 0.4321, q^2_se = 0.4766, pred_r^2 = 0.7642, pred_r^2se = 0.2177, Z_{Score} $Q^{\wedge 2}$ = 0.9653, Best Rand $Q^{\wedge 2}$ = 1.2154.

3D QSAR model 4 The kNN-MFA contour plots (Fig.(1c)), is validated on the compounds comprising the test set and biological activities of test molecules are predicted. Model are the steric and electrostatic, hydrophobic field energy of interactions between probe (CH_3) and compounds at their corresponding spatial grid points of S_830, E_46, E_315,H-503.The external predictability of the above 3D-QSAR model using the test set was determined by Pred_r^2, which is 0.7642 and F value of 51.326 and number nearest neighbors *k* of 4 were observed with this model. It uses 1 steric, 2 electronic and one hydrophobic descriptors with 4 k nearest neighbor to evaluate activity of new molecule. The model is validated by á_ran_q2 = 0.00001, best_ran_q^2 = 1.2154 and Zscore_ran_q^2 = 0.9653. The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance.

In the QSAR model, steric descriptors with positive coefficients represent regions of high steric tolerance; bulky substituent is favourable in this region. Steric descriptors with positive coefficients indicate regions where less bulky substituent is disfavoured. Electrostatic field descriptors with negative coefficients represent regions that electronegative (electron-rich or electron-donating) groups are favourable in this region. To ascertain the true predictivity of the model, applying leave-one-out method of cross validation using weighted k-nearest neighbor was performed for all the analysis. it is observed that electrostatic field with positive coefficient (H_503) is far from the pyrimidin-4-ones moiety and possibly it has hardly any effect on the substituent nature.

Model-5 Simulated Annealing Variable Selection: pIC_{50}= 0.9632 + 25.1913 (S_830) + 2.7809 (E_221) -0.0373 (S_46) +0.0552 (H_503) + 1.5439

$N_{training}$ = 9, N_{test} = 3, Optimum Components = 4, DF = 24, r^2 = 0.8364, q^2 = 0.6845, F test = 38.438, r^2_se = 0.4321, q^2_se = 0.4814, pred_r^2 = 0.7328, pred_r^2se = 1.4871, Z_{Score} $Q^{\wedge 2}$ = 0.9653, Best Rand $Q^{\wedge 2}$ = 1.2154.

The kNN-MFA contour plots (Fig.(1d)), which showed the relative position and ranges of the corresponding important electrostatic/steric fields in the model, provided guidelines for new molecule design . As far as steric field is concerned, a negative range indicated that a negative steric potential was favourable for increased activity and hence a less bulky substituent group was preferred in that region. Freedom of an amide N-H bond R_1, R_2, R_3 position compared to an acyclic C-H bond is required for activity; the presence of less bulky groups on the benzene ring would increase the activity.

Model are the steric and electrostatic, hydrophobic field energy of interactions between probe (CH_3) and compounds at their corresponding spatial grid points of S_830 , E_221 , S_46 ,H-503. The external predictability of the above 3D-QSAR model using the test set was determined by Pred_r^2, which is 0.7328and F value of 38.438 and number nearest neighbors k of 4 were observed with this model. The increase in negative value of S_46 indicates that aromatic substituent should be less bulky for optimum activity as in case of compounds.

CONCLUSION

From the QSAR studies descriptors (HOMO, logp, DPL, CAA, Ovality) were found as the important factor for the Ang II activity. These descriptors described the thermodynamic and steric properties of compounds. The QSAR model used was Hansch type model and for the statistical analysis the multiple linear regression analysis technique was used. HOMO and Dipole moment are electronic descriptors. HOMO is the highest occupied molecular orbital called frontier orbital and determines the way it interacts with other species. HOMO is the orbital that could act as an e-donor. Since it is outermost (highest energy), the negative contribution of HOMO energy suggested that substitution of group at pyrimidin-4-ones moiety with electron withdrawing group favourable for the antihypertensive activity in the concerned microbes. Dipole moment is the electrical dipole for a pair of opposite charges of electrons. Polar molecule creates dipole due to separation of charge. Electron donating group decreases the dipole moment hence increases the activity. Ovality is the ratio of molecular surface area to the minimum surface area. The minimum surface area is the surface area of a sphere having a volume equal to the solvent excluded volume of the molecule .Computed from the Connolly molecular surface area & solvent excluded volume properties, bulkiness of the molecule increases the ovality hence increases the antihypertensive activity. For 3D QSAR studies by kNNMFA methods steric field is concerned, a negative range indicated that a negative steric potential was favourable for increased activity and hence a less bulky substituent group was preferred in that region. Electrostatic field descriptors with negative coefficients represent regions that electronegative (electron-rich or electron-donating) groups are favourable in this region.

REFERENCES

1. Ferrario, C.M., 1990. The Renin-Angiotensin System: Importance in Physiology and Pathology. J. Cardiovasc. Pharmacol., 15(3): 51-55.
2. Wexler, R.R., W.J. Greenlee, J.D. Irvin, M.R. Goldberg, K. Prendergast, R.D. Smith, P.B.M.W.M. Timmermans, 1996. Nonpeptide Angiotensin II Receptor Antagonists: The Next Generation in Antihypertensive Therapy. J. Med. Chem., 39: 625-656.
3. Dzau, V.J. and G.H. Gibbons, 1987. Autocrine and paracrine mechanisms of vascular myocytes in systemic hypertension. Amer. J. Cardiol., 60: 991-1031.
4. Griffin, S.A., W.C. Brown, F. MacPherson, J.C. McGrath, V.G. Wilson, N. Korsgaard, M.J. Mulvany and A.F. Lever, 1991. Angiotensin II causes vascular hypertrophy in part by a non-pressor mechanism. Hypertension. 17: 626-635.
5. Weber, K.T., Y. Sun and S.E. Campbell, 1995. Structural remodelling of the heart by fibrous tissue: Role of circulating hormones and locall produced peptides. Eur. Heart. J., 16: 12-18.
6. Kubinyi, H., R. Mannhold, L.R. Krogsgaard and H.E. Timmerman, 1993. Methods and principles in medicinal chemistry, vol 1. VCH, Weinheim, pp: 91-95.
7. Ajmani, S., K. Jhadav and S.A. Kulkarni, 2006. Three-dimensional QSAR using k-nearest neighbor method and its interpretation. J. Chem. Inf. Model., 46: 24-31.
8. Belvisi, L., G. Bravi. G. Catalano, M. Mabiliab, A. Salimbeni and C. Scolastico, 1996. A 3D QSAR CoMFA study of nonpeptide angiotensin II receptor antagonists. J. Comput. Aided. Mol. Des., 10: 567-582.
9. Sharma, M.C., D.V. Kohli, S.C. Chaturvedi and S. Sharma, 2009. Molecular Modeling Studies of Some substituted 2-butylbenzimidazoles angiotensin II receptor antagonists as antihypertensive agents. Digest. J. Nanomat. Biostruct., 4(4): 843-856.
10. Sharma M.C., S. Sharma, N.K. Sahu and D.V. Kohli, 2011. 3D QSAR kNNMFA studies on 6-Substituted Benzimidazoles Derivatives As Nonpeptide Angiotensin II Receptor Antagonists: A Rational Approach to antihypertensive agents. Jour. Saud. Chem. Soc., (In press)

11. Sharma, M.C., S. Sharma, N.K. Sahu and D.V. Kohli, 2011. QSAR Studies of some Substituted imidazolinones Derivatives angiotensin II receptor antagonists using Partial Least Squares Regression (PLSR) Based Feature Selection. Jour. Saud. Chem. Soc., (In press)
12. Yan, P.Z., B.C. Chen, H. Shi, H.J. Jian, L.W. Hai, L.S. Guo and Q.Y. Ru, 2007. QSAR study of angiotensin II antagonists using robust boosting partial least squares regression. Anal. Chim. Acta., 593: 68-74.
13. Venkatesan, A.M., J.I. Levin, J.S. Baker, P.S. Ghan, T. Bailey and J. Coupet, 1994. Substituted 4H-pyrido [l, 2-a] pyrimidin-4-ones Angiotensin II Receptor Antagonists. Bioorg. Med. Chem. Lett., 4(1): 183-188.
14. CS Chem office version 7.0, Cambridge Soft corporation, software publishers Association, 1730 M street, NW,Suite 700, Washington D.C.20036 (2002), 452-1600 USA.
15. Gupta, A.K., B.M. Arockia and S.G. Kaskhedikar, 2004. VALSTAT: A Program for Quantitative Structure Activity Relationship Studies and their validations. Indian. J. Pharm. Sci., 66: 396-402.
16. Vlife MDS software package, version 3.5, supplied by Vlife science technologies Pvt. Ltd, 1, Akshay 50, Anand park, Aundh, Pune, India. 411007.
17. Halgren, T.A. and R. Nachbar, 1996. Merck molecular force field. IV. Conformational energies and geometries for MMFF94. J. Comput. Chem., 17: 587-615
18. Gasteiger, J. and M. Marsili, 1980. Iterative partial equalization of orbital electro negativity- a rapid access to atomic charges. Tetrahedron., 36: 3219-3228.
20. Wold, S., 1978. Cross-validatory estimation of the number of components in factor and principal component models. Tetrahedron., 20(4): 397-405.
21. Sharma, M.C. and S. Sharma, 2010. 3D- Quantitative Structure-Activity Relationship Analysis of Some 2-Substituted Halogen benzimidazoles Analogues with Antimycobacterial activity. Int. J. Chem. Tech. Res., 2(1): 606-614.
22. Sharma M.C. S. Sharma. D.V. Kohli and S.C. Chaturvedi, 2010. Three Dimensional Quantitative Structural-Activity Relationship (3D-QSAR) Studies some 3-{4-[3-(2-aryl-phenoxy) butoxy]-phenyl} Propionic acids as novel PPAR γ/δ agonists. Der. Pharma. Chemica., 2(1): 82-90 .
23. Sharma M.C. S. Sharma. D.V. Kohli and S.C. Chaturvedi, 2010. QSAR and k-Nearest Neighbour Molecular Field Analysis (k-NN MFA) Classification Analysis of Studies of Some Bemzimidazoles Derivatives Antibacterial activity Against Escherichia coli. Der. Pharmacia. Lett., 2(1): 150-161.