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3D QSAR Studies on a Series of Sulfonylcarbamate Isostere Derivatives as Non-Peptide Angiotensin II Receptor Antagonists: kNNMFA Method

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Abstract: In this paper we reported 3D QSAR studies for the sixteen molecules of sulfonylcarbamate isostere derivatives by using 3D-QSAR studies were performed using the stepwise variable selection k-nearest-neighbor molecular field analysis approach; combined with various selection procedures, a leave-one-out cross-validated correlation coefficient (q^2) of 0.8632 and a non-cross-validated correlation coefficient (r^2) of 0.9043 were obtained and exhibited good external prediction with pred_ r^2 of 0.8036. The steric and electrostatic descriptors at the grid points E_611, S_683, S_462, E_243, E_396, E_546 and S_181 play an important role in the design of new molecule. Molecular field analysis was applied for the generation of steric and electrostatic descriptors based on aligned structures. Partial least-squares (PLS) method was applied for QSAR model development considering training and test set approaches. Successful implementation of a predictive QSAR model largely depends on the selection of a preferred set of molecular descriptors that can signify the chemico-biological interaction. Stepwise variable selection (SW) and simulated annealing (SA) are applied as variable selection methods for model development. To achieve this objective quantitative structure-activity relationship (QSAR) study was carried as it provides the rationale for the changes in the structure to have more potent analogs.

Key words: Ang II · Sulfonylcarbamate · kNNMFA · Partial least square (PLS)

INTRODUCTION

The vasoactive hormone angiotensin II (Ang II) produced by the renin-angiotensin system (RAS) is a potent regulator of blood pressure homeostasis, fluid volume and electrolyte balance in mammals [1]. The clinical success achieved by angiotensin converting enzyme (ACE) inhibitors in the treatment of hypertension and congestive heart failure has made the RAS a major focus for the discovery of novel antihypertensive agents [2].The renin-angiotensin system (RAS) and the sympathetic nervous system (SNS) are important regulators of cardiovascular function. Angiotensin II (Ang II), the effector peptide of RAS, elicits potent vasoconstrictor effects on interacting with specific Ang II receptors in vascular smooth muscle. A family of angiotensin peptides principally, Ang I Ang II are generated from a single precursor protein, angiotensinogen, by the actions of renin, angiotensin converting enzyme, chymases and various carboxy and amino-peptidases. The compounds which block Ang II receptors can be employed for the treatment of hypertension and Congestive Heart Failure [3]. Based on the literature survey, number of compounds has been reported showing antihypertensive activity [4-6]. Many different approaches to QSAR including 3D models have been developed since Hansch's seminal work, the cardinal point of which is the use of structural descriptors. The kNN MFA, used for 3D QSAR analysis of the present data set adopts a k-nearest neighbour principle for generating relationships of molecular fields with the experimentally reported activity. The most popular 3D QSAR methods are comparative molecular field analysis (CoMFA) [7] and comparative molecular similarity analysis (CoMSIA) [8]. 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 [9].A number of quantitative structure-activity relationship (QSAR) studies related to design of antihypertensive drugs have also been reported so far [10-14] but a systematic QSAR study is yet to be carried out for angiotensin II receptor.The present study is aimed to elucidate the structural features of sulfonylcarbamate

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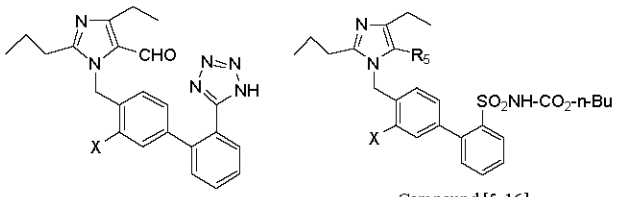
isostere derivatives required for angiotensin II receptor antagonists and to obtain predictive three-dimensional QSAR models to guide the rational synthesis of novel antihypertensive molecules. In the present investigation, three widely used techniques, viz. stepwise (SW) forward variable selection method and simulated annealing (SA) have been applied for descriptor optimization and partial least square (PLS) analysis has been applied for three-dimensional (3D) QSAR models development. The generated models provide insight into the influence of various interactive fields on the activity and, thus, can help in designing and forecasting the inhibition activity of novel antihypertensive molecules.

MATERIALS AND METHODS

Data Analysis: The Angiotensin II antagonist activity data of synthesized sulfonylcarbamate isostere derivatives were taken from the reported work [15]. The biological activity data (IC_{50} in nm) were converted to negative logarithmic dose (pIC_{50}) for quantitative structure activity analysis (Table 1). These models provide great relevance in design of novel Ang II antagonist not only in terms of predictivity, internally or externally, but also in terms of their ability to provide a chemical and structural explanation of their binding interaction and using descriptor 3D QSAR model describe Table 2. Our aim was to utilize these activity data for the development of a pvalid 3D-QSAR model based on steric and electrostatic fields that gives a deep insight into structure property activity correlations. All modelling studies (3D) were performed using the Molecular Design Suite (Vlife MDS software package, version 3.5; supplied by VLife Sciences, Pune, India) [16] on a Compaq PC with a Pentium IV processor and a Windows XP operating system. Structures were sketched using the 2D draw application and converted to 3D structures. Optimized molecules were aligned (Fig. 1) by template based method using the most active molecule as a template. Optimal training and test set were generated using the sphere exclusion algorithm [17] this algorithm allows the construction of training set covering the descriptor space occupied by representative points.

Molecular Modeling and Alignment: The 3D QSAR computations were carried out on a VLife QSAR plus 3.5; molecular modelling software. *In vitro* concentrations (IC_{50}) of the molecules were converted into corresponding pIC_{50} values (Table 1) and used as dependent variables in 3D QSAR calculations. Alignment of all the 16 compounds was done using template based alignment in MDS; the aligned structures were used for 3D QSAR studies. In template based alignment method, a template structure was defined and used as a basis for alignment of a set of molecules. Following sulfonylcarbamate molecule was the template used for template based alignment as it

Table 1: Chemical structure Sulfonylcarbamate compounds



Compound [1-4] Compound [5-16]

Comp	X	R_5	IC_{50}(nM)	pIC_{50}
1	F	-	7	0.845
2*	Cl	-	10	1.000
3	Br	-	20	1.301
4	CH_3	-	40	1.602
5	H	CHO	2	0.301
6*	CH_3	CHO	3	0.4771
7	F	CHO	0.7	-0.154
8	H	CO_2CH_3	2	0.3010
9*	NO;	CO_2CH_3	7	0.8450
10	Br	CO_2CH_3	2	0.3010
11	CH_3	CO_2CH_3	3	0.4771
12	Cl	CO_2CH_3	3	0.4771
13	F	CO_2CH_3	0.6	-0.221
14*	H	$COCH_3$	2	0.3010
15	CH_3	$COCH_3$	2	0.3013
16	Cl	$COCH_3$	6	0.77815

Table 2: Description of descriptor used in the 3D QSAR study

E_243	E_396	E_422	E_546	E_611	S_181	S_298	S_303	S_734
-0.07551	-0.07185	-0.06304	-0.05125	-0.03935	-0.00405	-0.00536	-0.00607	-0.00572
-0.00783	-0.00779	-0.00598	-0.03294	0.00144	-0.00417	-0.0057	-0.00663	-0.00632
-0.06726	-0.06212	-0.05263	-0.03988	-0.02649	-0.00459	-0.00592	-0.00643	-0.00578
0.001508	0.015405	0.029561	0.03987	0.04393	-0.00389	-0.00504	-0.00559	-0.00521
-0.05699	-0.06184	-0.063	-0.0611	-0.05739	-0.00366	-0.00471	-0.00521	-0.00487
-0.05675	-0.05679	-0.05514	-0.05271	-0.04966	-0.00378	-0.00495	-0.00557	-0.00528
-0.03577	-0.05419	-0.04586	-0.03481	-0.02379	-0.00393	-0.00513	-0.00571	-0.00531
-0.11664	-0.12298	-0.12085	-0.11095	-0.09621	-0.00378	-0.00494	-0.00551	-0.00513
-0.05432	-0.05794	-0.05914	-0.05858	-0.05657	-0.00385	-0.00504	-0.00567	-0.00534
-0.13841	-0.14596	-0.14296	-0.12978	-0.11026	-0.00429	-0.00559	-0.00605	-0.00537
-0.16495	-0.17221	-0.1678	-0.15301	-0.13206	-0.00489	-0.00671	-0.0076	-0.00688
-0.14481	-0.1469	-0.13897	-0.1229	-0.10276	-0.00544	-0.00753	-0.00843	-0.00743
-0.16153	-0.16198	-0.15158	-0.13242	-0.10901	-0.00481	-0.00636	-0.00691	-0.00606
-0.09379	-0.08934	-0.07944	-0.06565	-0.05065	-0.00494	-0.00654	-0.00713	-0.00629
-0.11819	-0.12945	-0.13422	-0.13076	-0.11964	-0.00458	-0.00597	-0.00651	-0.00583
-0.15515	-0.16492	-0.16372	-0.15188	-0.13297	-0.00458	-0.00608	-0.00676	-0.00613

Table 3: the unicolumn statistical analysis

Column Name	Average	Max	Min	Std.Dev
Training set	65.867	13.1652	9.5431	2.8754
Test set	23.691	7.65438	4.7654	0.6540

Table 4 Probe setting for 3D QSAR Studies

S.No	From	To	Interval
X	-12.7643	15.6543	2.0000
Y	-9.69532	8.17654	2.0000
Z	-6.56785	6.07653	2.0000

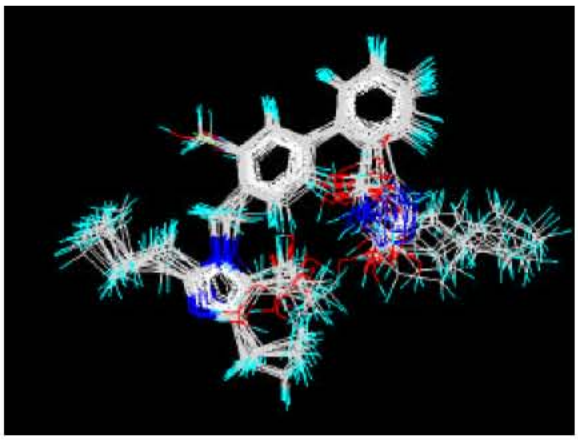


Fig. 1: Aligned molecules

was common to all structures. All the16 molecules were aligned with the template in this study and were used in 3D QSAR study. The optimal test and training data sets were generated using sphere exclusion method. This algorithm covering all descriptor space occupied by representative point. The dissimilarity level was set to 9.1, as the higher the dissimilarity level, the lesser the predictive ability of QSAR model, the method resulted in selection of four compounds as test set and remaining others as a training set. The set data was observed for activity distribution as activity distribution plot which revealed that almost all the compounds in test set are within the minimum maximum limit of the training set (Table 3). The observed selection of test set molecules was made by considering the fact that test set molecules represents a range of biological activity similar to the training set. The careful analysis of comparison of biological activities (pIC_{50}), predicted activities for training and test set molecules indicate very less significant differences (lower values of residuals). Therefore it can be said that the predictive abilities of SW kNN MFA model is good. 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 sp^3 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 to generate steric field energies and electrostatic fields. For calculation of field descriptor values, using Tripos force field[18] both electrostatic and steric field types, with cut-offs of 10.0 and 30.0 kcal/ mol, respectively, were selected and charge type was selected as by Gasteiger and Marsili. The dielectric constant was set to 1.0 considering the distance-dependent dielectric function. Molecular fields are the steric and electrostatic field interaction energies which are used to formulate a relationship between steric and electrostatic properties together with the biological activities of compounds. Probe setting was carbon atom with charge 1.0 and grid setting (Table 4).This resulted in calculation of 2400 field descriptors (1200 for each electrostatic and steric) for all the compounds in separate columns. QSAR analysis was performed after removal of all the invariable columns, as they do not contribute to the QSAR.

Stepwise (SW) variable selection method the kNN-MFA model for all the antihypertensive activities was developed using stepwise forward backward method with cross correlation limit set to 0.5 and term selection criteria as q^2. F-test 'in' was set to 4.0 and F-test 'out' to 3.99. As some additional parameters, variance cutoff was set as 2 Kcal/mol A^0 and scaling and auto scaling, additionally the k-nearest neighbor parameter setting was done within the range of 2-5 and prediction method was selected as distance base weighted average. The method resulted in the models which described as the graph between observed and predicted activities of test and training set for each activity was obtained as 'fitness plot'.

Simulated annealing (SA) kNN-MFA models for all the antihypertensive activities were also developed using simulate annealing as variable selection method. the cross correlation limit was set as 0.5, maximum temperature as 100, minimum temperature as 0.01, iteration at given temperature as 5, decrease temperature by as 10, seed as 0, perturbation limit as 1 and term selection criteria as q^2. Models were generated by KNN-MFA in conjunction with stepwise (SW) forward-backward and simulated annealing (SA) variable selection method for the selected member of training and test sets. The software Vlife MDS

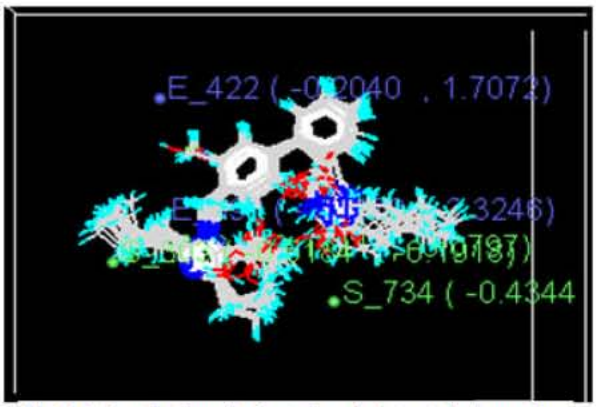


Fig. (2a). Contribution plot for steric and electrostatic interactions Stepwise (SW) variable selection method

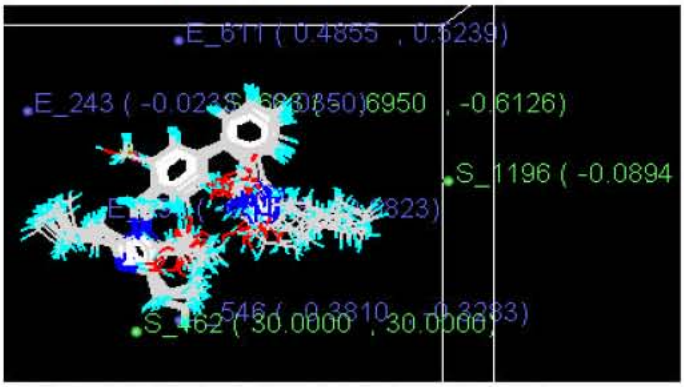


Fig. (2b). Contribution plot for steric and electrostatic interactions Simulated annealing (SA) method

Fig. 2(a,b): Contribution plot for steric and electrostatic interactions

3.5 allow user to choose probe, grid size and grid interval for the generation of descriptors.

RESULTS AND DISCUSSION

QSAR Studies were performed using VLife Molecular Design Suite software [19-21]. The QSAR models were evaluated using following statistical measures: *n*, number of observations (molecules); Vn, number of descriptors; *k*, number of nearest neighbours; q^2, cross validated r^2 (by the leave-one-out method); pred_r^2, predicted r^2 for the external test set; Z_{score}, the Z_{score} calculated by q^2 in the randomization test; best_ran_q^2, the highest q^2 value in the randomization test; and R, the statistical significance parameter obtained by the randomization test.

Stepwise (SW) Variable Selection Method (Model-1): pIC_{50}=-0.20421 (E_422)-0.5184 (S_303) + 0.3478 (E_396)-0.4344 (S_734)-0.1114(S_298) +1.983 n= 16, Optimum Components = 4, DF = 24, r^2 = 0.8518, q^2 = 0.7743, F test = 66.4165, r^2_se = 0.3276, q^2_se = 0.4762, pred_r^2 = 0.7216, pred_r^2se = 0.3760, Z_{Score} $Q^{\wedge 2}$ = 6.32651, Best Rand $Q^{\wedge 2}$ = 0.1476.

The descriptors E_422, S_303, E_396, S_734 and S_298 are the steric and electrostatic field energy of interactions between probe (CH_3) and compounds at their corresponding spatial grid points of 422, 303,396,734 and 298. The plot of observed versus predicted activity for the training and test sets of compounds in both the cases. The steric (S) and electrostatic (E) descriptors specify the regions, where variation in the structural features of different compounds in the training set leads to increase or decrease in activities. The number accompanied by the descriptors represents its position in the 3D MFA grid. The statistically best significant model (equation) using the SW-PLS analysis method with 0.8518 as the coefficient of determination (r^2) and standard error (SE) of 0.4359 was considered. The variance in the observed activity values is 85.18%. The best q^2 of PLS analysis was found to be 0.7743 which suggests that the model could be useful for predicting Ang II activity for such derivatives Compounds. In stepwise (SW) forward variable selection algorithm, the search procedure begins with developing a trial model step by step with a single independent variable and to each step; independent variables are added one at a time, examining the fit of the model by using the PLS cross-validation procedure. The variance cutoff was set at 0.5 and auto scaling in which the number of random iterations was set at 600. The steric and electrostatic contributions were 68 and 32 %, respectively and exhibited good external prediction with r^2 *pred* of 0.7216. Descriptor range for the selected model of the Series elaborates that negative range of descriptors S_303, S_734, S_298 steric field indicates that less bulky substituent would be favourable for the activity. Positive range of electronic field E_396 indicates that less electronegative substituent would be favourable for the activity as already the basic moiety taken in the study is substituted with high electronegative groups like chlorine and fluorine so the other substituents employed should be less electronegative. Negative range value of descriptors reveals that E_422 electrostatic indicates that less electronegative substituent would be favourable for the activity. Whereas negative coefficient indicates that electronegative (electron-rich or electron-donating) groups are favorable in this region. The standard leave-one-out (LOO) procedure was implemented to calculate cross validated r^2 (q^2) value, that is a molecule in the training set was eliminated and its biological activity was predicted as the weighted average activity of the k most similar molecules. The plot of observed versus predicted activities for the test compounds is represented in Fig.3 (a), Table 5 it is evident that the predicted activities of all the compounds in the test set are in good agreement with their corresponding experimental activities and optimal fit is obtained.

Table 5: Calculated and Predicted pIC_{50} (by LOO method)

Comp	Observed activity	Model Predict-1	Model Predict-2
1	0.845	1.102	1.0875
2	1.000	0.9914	0.3789
3	1.301	1.1765	1.4364
4	1.602	1.4132	1.6958
5	0.301	0.4321	0.3175
6	0.4771	0.3070	0.4598
7	-0.154	0.0574	-0.2175
8	0.3010	0.4476	0.2958
9	0.8450	0.9032	0.8594
10	0.3010	0.2895	0.3215
11	0.4771	0.4894	0.4789
12	0.4771	0.4560	0.4561
13	-0.221	-0.2458	-0.2346
14	0.3010	0.3187	0.2951
15	0.3013	0.3342	0.3138
16	0.77815	0.7832	0.7509

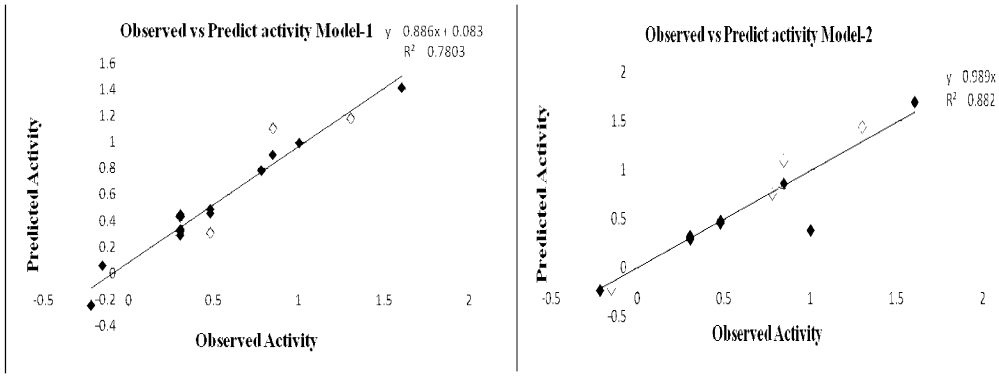


Fig. 3: Graphs of observed vs. predicted activity of models 1 and 2

Simulated Annealing (SA) Method (model-2): pIC_{50}= 0.4855 (E_611)-0.6950 (S_683) + 30.0000 (S_462)-0.0233 (E_243)-0.3478 (E_396)-0.3810 (E_546)-0.0124 (S_181) +0.5467 n= 16, Optimum Components = 4, DF = 22, r^2 = 0.9043, q^2 = 0.8632, F test = 67.543, r^2_se = 0.1443, q^2_se = 0.4866, pred_r ^{2}= 0.8036, pred_r se^2= 0.5763, ZScore $Q^{\wedge 2}$ = 2.54320, Best Rand $Q^{\wedge 2}$ = 1.8765.

Model-2, [Figure-2(b)] the kNN-MFA model generated from template based alignment showed the calculation of the pair wise molecular similarities and hence the prediction was based upon current training set, the q^2 value obtained 0.8632 is the indicative power of the current kNN-MFA model. The above steps were repeated for q^2 (cross validated r^2) of with four descriptors namely E_611, S_683, S_462, E_243, E_396, E_546 and S_181. Steric and electrostatic field energy of interactions between probe (CH_3) and compounds at their corresponding spatial grid points of 611, 683, 462,243,396,546 and 181.A non-cross validated *r2* of 0.9043, *F* value of 67.543 and number nearest neighbors *k* of 4 and degree of freedom 22 were observed with this model. The steric and electrostatic contributions were 25 and 75 respectively and exhibited good external prediction with r^2 *pred* of 0.8036.Statistical significance of the model indicated by *Z score* value of 2.54320 and *á* of >0.0001.As far as S_683, S_181 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. In the QSAR model, S_462 steric descriptors with positive coefficients represent regions of high steric tolerance; bulky substituent is favorable in this region. Steric descriptors with negative coefficients indicate regions where bulky substituent is favoured. E_243, E_396 and E_546 electrostatic field descriptors with negative coefficients represent regions where electronegative groups are favourable and E_611 electrostatic field descriptors with positive coefficients represent regions where electropositive (electron-withdrawing) groups are unfavourable. The plot of observed versus predicted activities for the test compounds is represented in Table 5 and fig 3(b).

CONCLUSION

In this work, we successfully aligned structures of sulfonylcarbamate derivatives as angiotensin II receptor antagonists which are minimized by molecular mechanics using standard MMFF force field for the kNN-MFA study. Descriptors with no variation were removed from the data. Number of descriptors necessary and sufficient for the QSAR equation was first determined. The negative range of steric descriptors indicate that negative steric potential is favorable for activity and less bulky substituent is preferred in that region. Positive value of steric descriptors reveal that positive steric potential is favorable for increase in activity and more bulky group is preferred in that region. Electrostatic field descriptors with negative coefficients represent regions where electronegative groups are favourable, electrostatic field descriptors with positive coefficients represent regions where electropositive (electron-withdrawing) groups are unfavourable.

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