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3D Qsar Studies on Series of 2, 3-Dihydro-4(1H)-quinazolinone Derivatives Angiotensin II Receptor Antagonists: *kNNMFA Approach*

Mukesh Chandra Sharma and Dharm Veer Kohli

Department of Pharmaceutical Sciences,
Dr. H.S. Gour University, Sagar (M.P.) 470 003, India

Abstract: The k-Nearest Neighbor Molecular Field Analysis (kNN-MFA), a three dimensional quantitative structure activity relationship (3D-QSAR) method has been used in the present case to study the correlation between the molecular properties and the angiotensin II activity on a series of 2, 3-Dihydro-4(1H)-Quinazolinone derivatives. kNNMFA calculations for both electrostatic, steric field and hydrophobic were carried out. The master grid maps derived from the best model has been used to display the contribution of steric, electrostatic potential and hydrophobic field. The q^2, pred_r^2, V_n and k value of kNN-MFA with SA, SW and GA. although there are no common descriptors among these three other methods, stepwise method kNN-MFA 3D QSAR best model H_537, S_396, E_998, E_377, E_535 and S_70 have better q^2 0.8954 and pred_r^2 0.81495 than other two methods, model validation correctly predicts activity 81 % and 80 % for the training and test set respectively. Contour maps using this approach showed that steric, electrostatic and hydrophobic field effects dominantly determine binding affinities. The information rendered by 3D QSAR models may lead to a better understanding of structural requirements of Angiotensin II receptor and can help in the design of novel potent molecules.

Key words: Ang II, 2, 3-Dihydro-4(1H)-Quinazolinone · 3D QSAR · Losrtan · kNN-MFA

INTRODUCTION

The octapeptide angiotensin II (Ang II) is produced by the renin angiotensin system (RAS) and is a potent vasoconstrictor and thus plays an important role in the pathophysiology of hypertension [1]. The octapeptide angiotensin II (Ang II, Asp-Arg-Val-Tyr-Ile-His-Pro-Phe), an important hormone in the renin-angiotensin system, exerts its action by activation of AT_1 and AT_2 receptors. The two receptor types are both G-protein coupled receptors, but they differ considerably by exhibiting a sequence homology of only 32-34% by having distinguished signaling pathways and by having different physiological effects [2-4]. Two distinct subtypes of the Ang II receptor labelled as AT_1 and AT_2 are known. Numerous studies in the past few years have shown that the major biochemical and functional responses of Ang II are mediated by activation of the AT_1 receptor. Angiotensin II (Ang II), a potent vasoconstrictive hormone formed within the RAS cascade, is implicated in the increase of the arterial blood pressure. Drug design for developing novel synthetic antihypertensive drugs were targeted either to the inhibition of AII biosynthesis (renin or angiotensin converting enzyme (ACE) inhibitors) or to the antagonism of AII binding to Angiotensin II (AT_1) receptors. Angiotensin II receptor blockers (ARBs) have been developed to produce a more complete blockade of the action of AII compared to other drug classes as well as an improved side effect profile [5,6]. Computational chemistry, prediction of biological activity based quantitative structure activity relationship (QSAR) substantially increases the potential of work, avoiding time and resource consuming experiments [7]. The most popular 3D-QSAR methods are comparative molecular field analysis CoMFA and comparative molecular similarity analysis CoMSIA [8, 9]. The CoMFA method involves generation of a common three-dimensional lattice around a set of molecules and calculation of the steric and electrostatic interaction energies at the lattice points while the CoMSIA method uses the similarity functions represented by Gaussian [10]. Newly reported method k-Nearest Neighbor Molecular Field Analysis (k-NN MFA)

Corresponding Author: M.C. Sharma, Department of Pharmaceutical Sciences, Dr. Hari. Singh. Gaur. University Sagar. 470003 (M.P) India. E-mail: mukeshcsharma@yahoo.com.

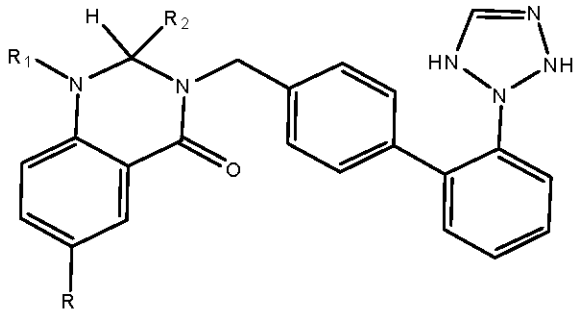
adopts a k-Nearest Neighbor principle for generating relationship of molecular fields with the experimentally reported activity. This method utilizes the active analogue principle that lies at the foundation of medicinal chemistry [11]. A number of quantitative structure-activity relationship (QSAR) studies related to design of angiotensin II receptor antagonists drugs have also been reported [12-16]. The present study is aimed to elucidate the structural features of 2, 3-Dihydro-4(1H)-Quinazolinone derivatives required for angiotensin II receptor antagonists and to obtain predictive three-dimensional QSAR models to guide the rational synthesis of novel inhibitors. In the present investigation, three widely used techniques, viz. stepwise (SW) forward variable selection method, genetic algorithm (GA) 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 novel antihypertensive molecules.

MATERIALS AND METHODS

Data Analysis: The Angiotensin II antagonist activity data of synthesized 2, 3-Dihydro-4(1H)-Quinazolinone derivatives were taken from the reported work [17]. The biological activity data (IC_{50} in μm) were converted to negative logarithmic dose ($-\log IC_{50}$) for quantitative structure activity analysis. Table 1 shows the structure of 19 such compounds along with their biological activity values. 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 is to utilize these activity data for the development of a valid 3D-QSAR model based on steric, electrostatic and hydrophobic fields that gives a deep insight into structure property activity correlations.

Geometry Optimization: The model developed using the training set was used to predict the activity of the compounds in the test set.All the molecular modeling

Table 1: Structural and biological data of 2, 3-Dihydro-4(1H)-Quinazolinone structures



Comp.	R	R^1	R^2	IC 50	pIC_{50}
1	H	H	Me	90	4.04576
2	H	H	Et	27	4.56864
3	H	H	iPr	0.54	6.26761
4*	H	H	nBu	14	4.85387
5	H	H	$(nBu)_2$	13	4.88606
6	Me	H	Et	20	4.69897
7	iPr	H	Et	45	4.34679
8	iPr	H	nPr	12	4.92082
9*	Et	H	nBu	0.37	6.43186
10	Bn	H	nBu	3.7	5.43183
11	iPr	H	nBu	0.09	7.04576
12	CO_2Me	H	nBu	4.1	5.38722
13*	H	Me	nBu	1.1	5.95861
14	H	Me	nPr	0.05	7.30103
15	H	Et	nPr	7.5	5.12494
16	H	Bn	nPr	100	4.00000
17*	iPr	Me	nBu	0.65	6.18709
18	$C(Me)_2OMe$	H	nBu	2.7	5.56864
19	$C(Me)_2OMe$	Me	nBu	2	5.69897

*test compound

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

H_67	H_176	H_537	E_535	E_998	E_444	S_70	S_396	S_882
0.211734	0.214455	0.211231	0.137041	0.099874	0.062457	-0.0315	-0.0466	-0.0609
0.308815	0.311217	0.309197	0.001074	0.000349	-0.05486	-0.0516	-0.087	-0.1291
0.320448	0.323411	0.319949	0.069894	0.055037	0.07628	-0.0296	-0.0451	-0.0061
0.231757	0.233436	0.231106	0.223748	0.190875	0.150077	-0.436	-0.0716	-0.1033
0.281459	0.285072	0.281974	0.092574	0.055079	0.020672	-0.2091	-0.0262	-0.0931
0.237889	0.240375	0.238024	0.074354	0.058258	0.040044	-0.0309	-0.0461	-0.0614
0.273245	0.27617	0.272941	0.077151	0.065854	0.052138	-0.0631	-0.0636	-0.0876
0.556587	0.560969	0.557285	0.035693	0.03318	0.02892	-0.0368	-0.0547	-0.0739
0.31471	0.318387	0.316214	0.04035	0.02579	0.013379	-0.0255	-0.0385	-0.0515
0.312282	0.315915	0.313238	-0.01106	-0.0241	-0.03302	-0.0351	-0.0584	-0.0858
0.306986	0.309856	0.306826	-0.02214	-0.04595	-0.05993	-0.0288	-0.0435	-0.0585
0.218669	0.220287	0.217351	0.072083	0.045497	0.020142	-0.0372	-0.0595	-0.0829
0.245705	0.248586	0.245849	0.102388	0.061982	0.026725	-0.023	-0.0338	-0.0442
0.256056	0.258891	0.256783	0.088551	0.072028	0.055307	-0.0307	-0.0454	-0.0595
0.339322	0.341787	0.337863	0.082414	0.065785	0.046845	-0.0302	-0.0457	-0.0613
0.228458	0.230785	0.228803	0.053315	0.010495	0.003237	-0.0671	-0.1198	-0.0862
0.290011	0.292838	0.289809	0.011118	0.007456	0.002616	-0.0121	-0.0098	-0.0152
0.293229	0.296212	0.293458	0.109089	0.087451	0.062633	-0.0168	-0.0252	-0.0463
0.325863	0.330017	0.325734	0.139416	0.100474	0.061343	-0.0496	-0.0114	-0.0777

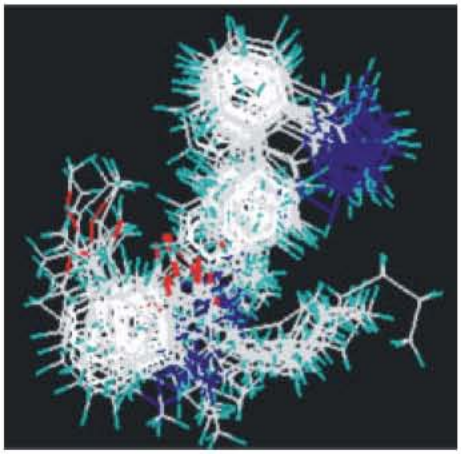


Fig. 1: Align molecules

studies (3D) were performed using Molecular Design Suite supplied by the VLife Sciences [18], Pune on Compaq PC having Pentium IV processor and windows XP operating system. The structures were sketched using the 2D draw application and converted to 3D structures. Three-dimensional structures were drawn for each molecule and the molecular geometries optimized using Monte Carlo conformational search, MMFF fields and charges. 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[19] .This algorithm allows the construction of training set covering the descriptor space occupied by representative points. A training set of 14 molecules and a test set of 5 molecules were generated. kNN-MFA with stepwise forward-backward, variable selection method was employed for selection of variables to obtain the QSAR model. 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.This process forms the basis of a technique known as feature selection [20] or variable selection. Among several search algorithms, stepwise (SW) forward variable selection method genetic algorithms (GA) [21]and simulated annealing (SA) [22] based feature selection procedures are most popular for building QSAR models and can explain the situation more effectively. 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. Thus, the model is repeatedly altered from the previous one by adding or removing a predictor variable in accordance with the 'stepping criteria' (in this case F = 4 for inclusion; F = 3.99 for exclusion for the forward-backward selection method). The method continues until there is no more significant variable remaining outside the model. In the selected equations, the cross-correlation limit was set at 0.5, the number of variables at 10 and the term selection criteria at r^2. An F value was specified to evaluate the significance of a variable. The variance cutoff was set at 0.0 and auto scaling in which the number of random iterations was set at 100.

Computation of Steric, Electrostatic and Hydrophobic Fields: For calculation of field descriptor values, using Tripos force field steric, electrostatic and hydrophobic fields type with cut offs 10.0 and 30.0 Kcal/mol respectively were selected and charge type was selected as Gasteiger-Marsili. Dielectric constant was set to 1.0 considering the distance dependent dielectric function. The aligned biologically active conformations of 2, 3-Dihydro-4(1H)-Quinazolinone are used for the calculation of molecular fields. Molecular fields are the steric, electrostatic and hydrophobic 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. This resulted in calculation of 6366 field descriptors (2122 for each electrostatic, steric and hydrophobic) for all the compounds in separate columns. QSAR analysis was performed after removal of all the invariable columns, as they do not contribute to QSAR. The optimal test and training data set were generated using manual selection method. In this method selection of five compounds as test set and remaining others as training set was done.

k-Nearest Neighbor (kNN) 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 neighbours 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: (1) calculate distances between an unknown object (u) and all the objects in the training set; (2) select k objects from the training set most similar to object u, according to the calculated distances and (3) 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. To derive the kNN-MFA descriptor fields, a 3D cubic lattice grid in x, y and z directions, was created to encompass the aligned molecules. kNN-MFA descriptors were calculated using an sp3 carbon probe atom with a van der Waals radius of 1.52 Å and a charge of +1.0 to generate steric field energies and electrostatic fields with the distance dependant dielectric at each lattice point. The steric and electrostatic energy values were truncated at a default value of 30 kcal/mol.

Evaluation of 3D QSAR ModelsThe developed QSAR models are evaluated using the following statistical measures: n, (the number of compounds in regression); k, (number of variables); DF, (degree of freedom); optimum component, (number of optimum PLS components in the model); r^2 (the squared correlation coefficient), F test (Fischer's value) for statistical significance, q^2 (cross-validated correlation coefficient); pred_r^2, (r^2 for external test set); Z score, (Z score calculated by the randomization test); best_ran_q^2, (highest q^2 value in the randomization test); best_ran_r^2, (highest r^2 value in the randomization test). The regression coefficient r^2 is a relative measure of fit by the regression equation. It represents the part of the variation in the observed data that is explained by the regression. However, a QSAR model is considered to be predictive, if the following conditions are satisfied: $r^2 > 0.6$, $q^2 > 0.6$ and pred_$r^2 > 0.5$. The F-test reflects the ratio of the variance explained by the model and the variance due to the error in the regression. High values of the F-test indicate that the model is statistically significant. The low standard error of Pred_r^2se, q^2_se and r^2_se shows absolute quality of fitness of the model.

Cross-validation Using Weighted K-nearest Neighbor Internal and External Validation: Internal validation is carried out using 'leave-one-out' (LOO) method . The cross-validated coefficient, q^2, is calculated using the following equation:

$$q^2 = 1 - \frac{\sum (y_i - \hat{y}_i)^2}{\sum (y_i - y_{\text{mean}})^2}$$

Where y_i and y_i are the actual and predicted activity of the i^{th} molecule in the training set, respectively and y_{mean} is the average activity of all molecules in the training set. However, a high q^2 value does not necessarily give a suitable representation of the real predictive power of the model for antimalarial ligands. So, an external validation is also carried out in the present study. The external predictive power of the model is assessed by predicting pIC_{50} value of the test set molecules, which are not included in the QSAR model development. The predictive ability of the selected model is also confirmed by pred_r^2 or rCVext^2.

$$\text{pred\_r}^2 = 1 - \frac{\sum (y_i - \hat{y}_i)^2}{\sum (y_i - y_{\text{mean}})^2}$$

where y_i and y_i are the actual and predicted activity of the i^{th} molecule in the test set, respectively and y_{mean} is the average activity of all molecules in the training set.

The robustness of the selected model is checked by Y - randomization test. The robustness of the models for training sets is examined by comparing these models to those derived for random datasets. Random sets are generated by rearranging the activities of the molecules in the training set. The significance of the models hence obtained is derived based on a calculated Z score . A Z_{score} value is calculated by the following formula:

$$Zscore = \frac{(h - \mu)}{\sigma}$$

where h is the q^2 value calculated for the actual dataset, ì the average q^2 and ó is its standard deviation calculated for various iterations using models build by different random datasets.

RESULTS AND DISCUSSION

All the nineteen compounds were built on workspace of molecular modelling software VLifeMDS; we hereby report the models, as generated by kNN-MFA in conjunction with simulated annealing (SA), genetic algorithm (GA) and stepwise (SW) forward variable selection methods in best molecules template. The unicolumn statistical analysis can be (Table 3) interpreted to mean that the maximum of the test is less than to maximum of training set and the minimum of the test is greater than minimum of the training set to have maximum and minimum activity in the training set to obtain structure diversity. It also shows that in all cases the test set was interpolative i.e. derived within the minimum-maximum range of the training set. The mean and standard deviation of the training and test sets provided an insight to the relative difference of mean and point density distribution (along mean) of the two sets. The mean of the test sets were higher than the training sets which indicates the presence of relatively more active molecules as compared to the inactive ones. Also, in both the cases a relatively higher standard deviation in training sets indicates that training sets had widely distributed activity of the molecules as compared to the test sets. In the kNN-MFA method, several models were generated for the given or selected members of training and test sets and the corresponding best models are reported herein. Which allows user to choose probe, grid size and grid interval for the generation of descriptors. The variable selection methods along with the corresponding parameters are allowed to be chosen and optimums models are generated by maximizing q^2.The kNN-MFA models provide direction for the design of new molecules in a rather convenient way. The points which contribute to the SA, SW and GA kNN-MFA models in all three data sets are displayed in figure. The range of property values for the chosen points may aid in the design of new potent molecules. The range is based on the variation of the field values at the chosen points using the most active molecule and its nearest neighbour set. . This method utilizes the active analogue principle that lies at the foundation of medicinal chemistry [23-25].

Table 3: the Unicolumn statistical analysis

	Average	Max Column Name	Min	Std Dev
Training set	85.0642	5.6709	7.3010	4.0000
Test set	17.6601	4.4150	4.6990	4.0458

Model-A Simulated Annealing: pIC_{50}= -6.7196 (E_535)+ 0.3216 (H_176)+ 30.000(S_396) -0.0333 (S_882)-0.0743 (S_665) -0.0075 (S_70)

$N_{traning}$ = 15, N_{test} = 4, Optimum Components = 4, DF = 24, r^2 = 0.8947, q^2 = 0.8458, F test = 54.7947, r^2_se = 0.4654, q^2_se = 0.7236, pred_r^2 = 0.7783, pred_r^2se = 0.2795, ZScore Q^2 = 8.5732, Best Rand Q^2 = 0.4876.

Model-B Stepwise (SW) Variable Selection: pIC_{50}=+0.7190 (H_537)+30.000(S_396)+ 0.0512 (E_998) - 7.0575 (E_377) -6.7196 (E_535) -0.0075 (S_70)

$N_{traning}$ = 15, N_{test} = 4, Optimum Components = 4, DF = 23, r^2 = 0.8597, q^2 = 0.8954, F test = 49.287, r^2_se = 0.3651, q^2_se = 0.6498, pred_r^2 = 0.81495, pred_r^2se = 0.6411, ZScore Q^2 = 2.0854, Best Rand Q^2 = 0.1541.

Model-C Genetic Algorithm: pIC_{50}= -7.6232 (E_444) - 0.0151(S_840) -0.0085 (S_10) to -0.0023)+ 0.2699 (H_67) - 3.5528 (E_552)- 0.0055 (S_70)

$N_{traning}$ = 15, N_{test} = 4, Optimum Components = 4, DF = 24, r^2 = 0.8354, q^2 = 0.7843, F test = 44.573, r^2_se = 0.8732, q^2_se = 0.4265, pred_r^2 = 0.7486, pred_r^2se = 0.4619, ZScore Q^2 = 7.5432, Best Rand Q^2 = 0.3328.

Model-A, best template used 3D QSAR based alignment shows a q^2 (cross validated r^2) of 0.8458 with six descriptors namely E_535, H_176,S_396,S_882, S_665 and S_70.Steric, electrostatic and hydrophobic field energy of interactions between probe (CH_3) and compounds at their corresponding spatial grid points of 535,176,396,882,665 and 70. Based QSAR model leads us to explain the effect of steric and electrostatic and hydrophobic fields on different substituents of dihydroquinazolinones moiety.

Table 4: Observed and predicted activities of statistically significant model obtained by kNN-MFA

S.No	Observed Activity	SA-Predict Activity	SW-Predict Activity	GA-Predict Activity
1	4.045	4.158	4.194	4.27
2	4.568	4.513	4.621	4.418
3	6.267	6.341	6.185	6.326
4	4.853	4.796	4.914	4.807
5	4.886	4.762	4.945	4.906
6	4.698	4.629	4.810	4.519
7	4.346	4.438	4.408	4.241
8	4.920	4.754	4.897	5.906
9	6.433	6.297	6.330	6.795
10	5.431	5.792	5.281	5.305
11	7.045	7.169	6.896	6.934
12	5.387	5.568	5.301	5.219
13	5.958	6.094	6.057	5.787
14	7.301	7.059	7.114	7.443
15	5.124	5.304	5.266	4.979
16	4.000	3.896	4.011	3.921
17	6.187	6.276	6.291	6.385
18	5.568	5.357	5.741	5.398
19	5.698	5.412	5.398	5.524

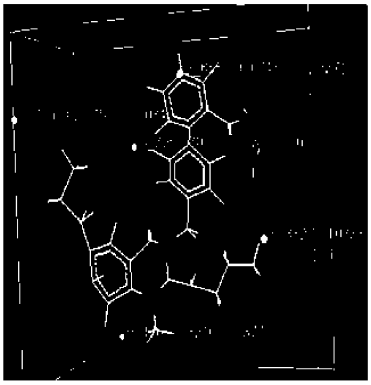


Fig.1(a). Contribution plot for steric electrostatic and hydrophobic interactions. Model-A **Simulated Annealing**

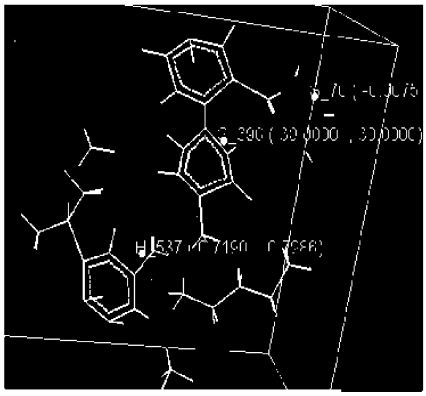


Fig. 1 (b). Contribution plot for steric, electrostatic and hydrophobic interactions.
Model-B **Stepwise (SW) Variable Selection**

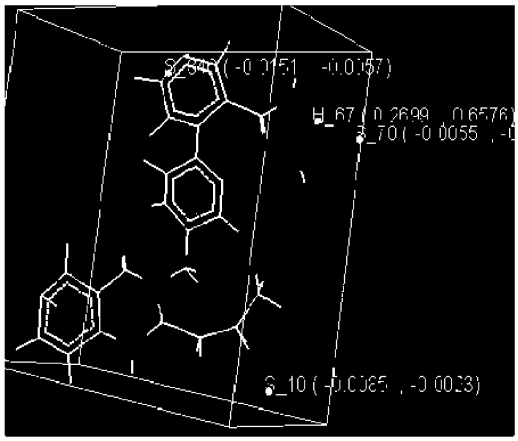


Fig.1 (c). Contribution plot for steric electrostatic and hydrophobic interactions.
Model-C **Genetic Algorithm**

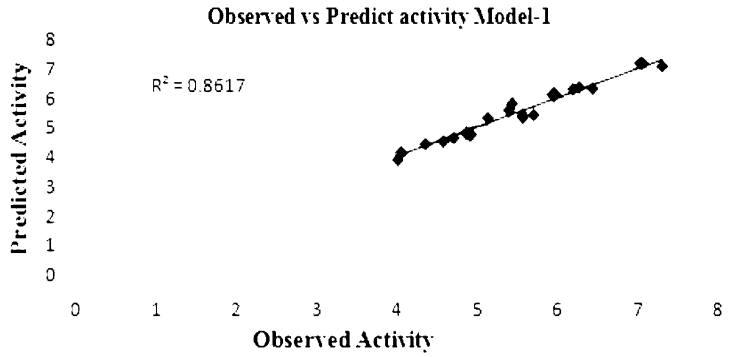


Fig. 2(a): Correlation plots of observed and predicted activities

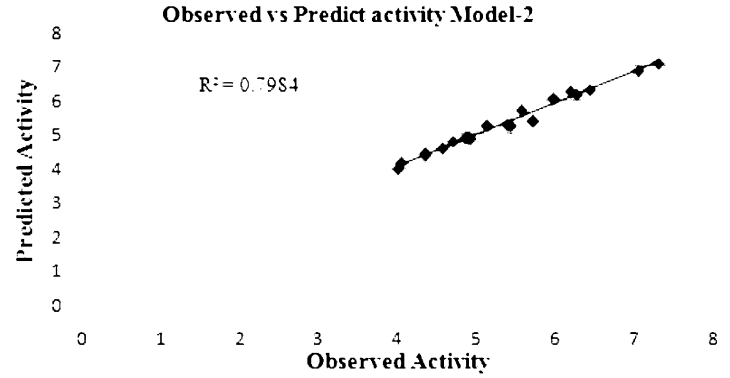


Fig. 2(b): Correlation plots of observed and predicted activities

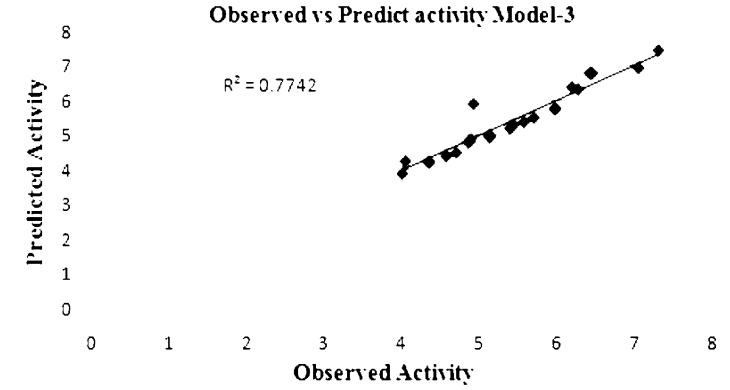


Fig. 2(c): Correlation plots of observed and predicted activities

A non-cross-validated r^2 of 0. 8947, F value of 54.7947 and number nearest neighbors k of 4 were observed with this model. i.e. all the values are proved statistically significant. The steric, electrostatic and hydrophobic contributions were 69, 14 and 17 %, respectively and exhibited good external prediction with r^2 *pred* of 0.7783. Statistical significance of the model indicated by *Z score* value of 8.5732 and α of >0.0001. The above model is validated by predicting the biological activities of the test molecules, as indicated in Table 4. The plot of observed versus predicted activities for the test compounds is represented in Fig. 2(a). From Table 4 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.The plot of contributions of steric,electrostatic field and hydrophobic

interactions (Fig. 1(a)) indicates relative regions of the local fields (steric, electrostatic and hydrophobic) around the molecules. Green, blue and yellow balls represent steric electrostatic field and hydrophobic effects, respectively. Model-B, best template 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 (0.8165) is the indicative power of the current kNN-MFA model. The above steps were repeated for k = 4 (upper limit of k is the total number of molecules in the data set). *q2* (cross validated r^2) of with six descriptors namely H_537 E_535, S_396, E_998, E_377 and S_70. Steric, electrostatic and hydrophobic field energy of interactions between probe (CH_3) and compounds at their corresponding spatial grid points of 537,535,396,998,377 and 70.A non-cross validated *r2* of 0.8597, *F* value of 49.287and number nearest neighbors *k* of 4 were observed with this model. The steric, electrostatic and hydrophobic contributions were 54,25 and 30 %, respectively and exhibited good external prediction with *r2 pred* of 0.8047.Statistical significance of the model indicated by *Z score* value of 2.0854 and α of >0.0001. The above model is validated by predicting the biological activities of the test molecules, as indicated in Table 4. The plot of observed versus predicted activities for the test compounds is represented in Fig. 2(b) and The plot of contributions of steric and electrostatic field interactions (Fig. 1(b)) Model-C,best template the kNN-MFA model generated from template based alignment showed *q2* (cross validated *r2*) of 0.7843 with five descriptors namely E_444, S_10, H_67, E_552 and S_70. A non-cross validated r^2 of 0.8354, *F* value of 44.573 and number nearest neighbors *k* of 4 were observed with this model. Steric, electrostatic and hydrophobic field energy of interactions between probe (CH_3) and compounds at their corresponding spatial grid points of 444, 10, 67,552 and 70, which showed the relative position and ranges of the corresponding important electrostatic/steric fields in the model, provided guidelines for new molecule design. From Table 4 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. The plot of contributions of steric and electrostatic field interactions (Fig. 1(c)). The above model is validated by predicting the biological activities of the test molecules, as indicated in Table 4. The plot of observed versus predicted activities for the test compounds is represented in Fig. 2(c). 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 C-N bond compared to an acyclic C-C bond is required for activity. The steric, electrostatic and hydrophobic contributions were 28,52 and 22 %, respectively and exhibited good external prediction with *r2 pred* of 0.7348.Statistical significance of the model indicated by *Z score* value of 7.5432and α of >0.0001.With the view of all above also based on the predictive (Table 4) ability of two kNN-MFA models, analysis. The q2, pred_r2, Vn and k value of kNN-MFA with SA, SW and GA were (0.7958, 0.7752) (0.6680, 0.6981) and (0.7982, 0.7348) although there are no common descriptors among these three methods, Genetic Algorithm kNN-MFA method have better q2 and pred_r2 than other two methods, model validation correctly predicts activity 71% and 77% for the training and test set respectively. The proposed models, due to the high internal and external predictive ability, can therefore act as a useful aid to the costly and time consuming experiments for determining the molar concentration of a compound required to achieve better angiotensin II receptor activity. In the QSAR model, steric descriptors with positive coefficients represent regions of high steric tolerance; bulky substituent is favorable in this region. Electrostatic field descriptors with positive coefficients represent regions where electropositive (electron- withdrawing) groups are favorable, whereas negative coefficient indicates that electronegative (electron-rich or electron-donating) groups are favorable in this region .The master grid obtained for the various kNN-MFA models show that negative value in electrostatic field descriptors indicates the negative electronic potential is required to increase activity and more electronegative substituents group is preferred in that position, positive range indicates that the group which imparts positive electrostatic potential is favorable for activity so less electronegative group is preferred in that region. The plot of contributions of steric electrostatic and hydrophobic field interactions indicates relative regions of the local fields (steric electrostatic and hydrophobic) around the aligned molecules. The developed QSAR models allow for an understanding the molecular properties/features that play an important role in governing the variation in the activities. In addition, this 3DQSAR study allowed investigating the influence of simple and easy to compute descriptors in determining biological activities that could highlight the key factors and may aid in the design of novel and potent molecules.

CONCLUSION

In conclusion, the model developed to predict the structural features of 2, 3-Dihydroquinazolinones reveals useful information about the structural features requirement for the molecule. In all three optimized models, Model A, B and C is giving very significant results. Negative value in electrostatic field descriptors indicates that negative electronic potential is required to increase activity and more electronegative substituents group is preferred in that position, positive range indicates that group that imparting positive electrostatic potential is favorable for activity so less electronegative group is preferred in that region. Negative range in steric descriptors indicates that negative steric potential is favorable for activity and less bulky substituents group is preferred in that region, Positive value of steric and hydrophobic descriptors reveals that positive steric potential is favorable for increase in activity and more bulky group is preferred in that region.

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