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3D QSAR Studies of Substituted-4(3H) Quinazolinones Derivatives as Angiotensin II Receptor Antagonists

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Abstract: The objective of this work was to investigate k-nearest neighbour molecular field analyses of 16 molecules substituted-4(3H) Quinazolinones derivatives as angiotensin II receptor antagonists. In this paper we reported a novel three-dimensional QSAR approach, kNN-MFA, developed based on principles of the k-nearest neighbor method combined with various variable selection procedures. The kNN-MFA approach was used to generate models by all three models and predict the activity of test molecules through each of these models. Using kNN-MFA approach 3D-QSAR models were generated; one of these models was selected on the basis of q2 and pred_r2 values. The 3D-QSAR studies were based on lowest energy conformer of most active compound (6), employing atom and template based alignment methods. The best model A describe pIC_{50}=2.9863 ,0.5528 (S_453) - 0.4392 (E_931) + 0.4875 (S_657) +0.4099 (H_229) -0.7084. The selected model had shown good internal and external predictivity for the training set of 12 molecules and test set of 4 molecules with validation (q^2) and cross validation (pred_r^2) values of 0.8271 and 0.8413, respectively. The potency of the substituted-4(3H) Quinazolinones was interpreted based on kNN-MFA steric, electrostatic and hydrophobic point distribution maps.

Key words: Ang II · 3D QSAR · kNN-MFA · piperidin-2-one · Antihypertensive

INTRODUCTION

The renin-angiotensin system (RAS) plays a key role in regulating cardiovascular homeostasis and electrolyte fluid balance in normotensive and hypertensive subjects [1]. Activation of the renin-angiotensin cascade begins with renin secretion from the juxtaglomerular apparatus of the kidney and culminates in the formation of the octapeptide angiotensin II (AII), which then interacts with specific receptors present in different tissues [2]. The peptide hormone Angiotensin II (Ang II) is known to play an important role in the regulation of blood pressure and salt-water homeostasis. Two distinct subtypes of the Ang II receptor labeled 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. The various antihypertensive regimens such as angiotensin converting enzyme inhibitors and renin inhibitors have several side effects and limitations. The Ang II antagonists on the other hand do not have these disadvantages and have become a globally accepted therapy for hypertension [3]. The main effects of AII are the regulation of blood pressure through vasoconstriction, thereby effecting an increase in vascular resistance, the regulation of volemia through the stimulated release of vasopressin and aldosterone, which induces saline retention and the regulation of the adrenocorticotropic hormone (ACTH). Thus, reducing the levels of Ang II by inhibition of one of the RAS enzymes or directly blocking the Ang II receptors is in theory a good approach for treating hypertension, confirmed by the success of angiotensin-converting enzyme (ACE) inhibitors as antihypertensive [4]. Substantial effort has been made to find renin inhibitors, although orally active agents have only recently been reported [5]. No less effort has been devoted to finding Ang II antagonists, which besides being the most direct way of controlling the RAS could have the additional advantage of lacking the side effects, such as cough and angioedema, observed with ACE inhibitors, as these are probably caused by partial inhibition of the cleavage of bradykinin [6]. Many

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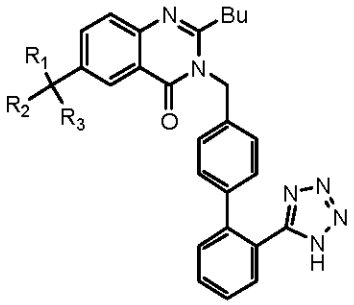
different approaches to QSAR have been developed over the years. The rapid increase in three-dimensional structural information (3D) of bioorganic molecules, coupled with the development of fast methods for 3D structure alignment (e.g. active analogue approach), has led to the development of 3D structural descriptors and associated 3D QSAR methods. The most popular 3D QSAR methods are comparative molecular field analysis (CoMFA) and comparative molecular similarity analysis (CoMSIA) [7-8]. In the present study; we have applied k-nearest neighbour molecular field analysis (kNNMFA) [9]. A number of quantitative structure-activity relationship (QSAR) studies related to design of angiotensin II receptor antagonists drugs have also been reported[10-13]. The present 3D QSAR study was carried out by using k-Nearest Neighbor Molecular Field Analysis (K-NNMFA) method for predicting the antihypertensive activity. The better the description of a molecule in terms of structural parameters representing its activity, the better the results of pattern recognition and separation of molecules by activity. The present communication is an attempt to explore the 3D QSAR of a series of substituted-(3H) Quinazolinones compounds. It aimed at explaining the observed variation in biological activity as a function of various electrostatics, steric and hydrophobic parameters and at predicting the best lead compounds for providing insight into substitutional and configurationally requirements for optimum receptor, leading to the development of the best pharmacological activity.

MATERIALS AND METHODS

The Ang II receptor antagonistic activity data of substituted-4(3H) Quinazolinones derivatives were taken from the reported work [14] and used for kNN-MFA analysis. The biological activities of these sixsitten compounds were expressed in terms of IC_{50} values for angiotensin II receptor antagonists. The biological activity values IC_{50} (nM) reported in nanomolar 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. The -log values of IC_{50} (pIC_{50}) along with the structure of the compounds in the series are listed in (Table 1).

Table 1: Biological activity data and structures of the compounds



Comp.	R_1	R_2	R_3	IC_{50}(nM)	pIC_{50}
1	H	H	OH	10	1.00
2	H	Me	OH	9	0.95
3*	H	Et	OH	12	1.08
4	Me	Me	OH	9	0.95
5*	H	H	NH_2	15	1.17
6	H	Me	NH_2	14	1.14
7	H	t-Bu	OH	>1000	3.00
8	H	CH_2OH	OH	>1000	3.00
9*	H	H	OMe	18	1.25
10	H	Me	OMe	7	0.84
11	H	Et	OMe	5	0.69
12	Me	Me	OMe	6	0.78
13	H	Ph	OMe	9	0.95
14*	H	Me	NHAc	6	0.78
15	H	H	OPh	130	2.11
16	H	H	O-2-Py	130	2.11

Table 2: Physicochemical parameters and indicator variable 3D QSAR Models

E_232	E_564	E_931	S_453	S_694	S_836	H_229
0.68138	0.39216	-0.1731	-0.0096	-0.0019	-0.00705	0.29187
0.70207	0.30492	0.01388	-0.0128	-0.002	-0.00742	0.45328
0.64925	0.33477	0.07489	-0.0186	-0.0017	-0.0066	0.44447
0.51407	0.27919	-0.0249	-0.0052	-0.0053	-0.00343	0.25433
0.61206	0.34035	-0.0517	-0.0119	-0.0022	-0.00631	0.28048
0.29946	0.16787	0.09476	-0.0047	-0.0085	-0.00263	0.22006
0.55471	0.32772	-0.0872	-0.0041	-0.0066	-0.00331	0.34886
0.09014	0.01561	0.06844	-0.0065	-0.0048	-0.00277	0.24565
0.98489	0.52201	-0.1161	-0.0306	-0.0019	-0.00939	0.43237
0.30138	0.17527	0.0528	-0.0046	-0.0082	-0.00282	0.32138
0.29565	0.17814	0.00412	-0.003	-0.0093	-0.00236	0.34355
0.12519	0.0423	0.04863	-0.0085	-0.003	-0.00446	0.31492
4.37948	1.30444	-0.075	-0.0732	-0.0012	-0.01148	0.33667
0.1825	0.08458	0.14448	-0.0045	-0.0078	-0.00274	0.22506
10.000	2.89882	-0.0361	-0.0682	-0.0013	-0.02185	0.27434
0.17824	0.11154	0.12221	-0.0045	-0.0053	-0.00705	0.34522

All the computational studies were performed on Compaq (Pentium-D) computer using the software VLife MDS 3.5[15]. Table 1 shows the structure of 16 such compounds along with their biological activity values. Substituted 4(3H) Quinazolinones as systematic variation of several substituents at the Quinazolinones ring positions R_1, R_2 and R_3 led. Out of these 16 compounds, small aliphatic substituents such as –Me, Et, -OH, NH_2, OMe, NHAc, CH_2OH,Ph and OPh, are attached at R_1, R_2 and R_3 -positions of compounds. The total set of inhibitors was divided into a training set (12 compounds) for generating 3D QSAR models and a test set (4 compounds) for validating the quality of the models. The training set and test set were selected manually by considering the fact that the test-set compounds represent structural diversity and a range of biological activities similar to that of the training set. In addition, the wide range of structural diversity of compounds in the test set permitted us to evaluate the extrapolative accuracy of the QSAR models. Selection of test set molecules was made by considering the fact that test set molecules represent structural features similar to compounds in the training set. Three-dimensional structures were drawn for each molecule and the molecular geometries optimized using Monte Carlo conformational search [16], which uses the metropolis condition to accept or discard generated conformers and energy minimization and geometry optimization were conducted using the Merck molecular force field (MMFF) [17] method with the root mean square (RMS) gradient set to 0.01 kcal/mol A and the iteration limit to 10,000. Optimal training and test set were generated using the sphere exclusion algorithm.The optimal training and test sets were generated using the sphere exclusion algorithm [18]. This algorithm allows the construction of training sets covering descriptor space occupied by representative points. The dissimilarity level was set to 5, as the higher the dissimilarity level, the lesser is the predictive ability of QSAR model. The selection of test and training set was further justified by unicolumn statistics calculated for each case of study. Once the training and test sets were generated, kNN methodology was applied to the descriptors generated over the grid. Complete geometry optimization was performed taking the most extended conformations as starting geometries.

Molecular Alignment: The most significant requisite for any 3D-QSAR study is to align the dataset on a suitable conformational template, either by taking a reported crystal structure of a bioactive compound or by considering the most active compound. In the present study, since we don't have any reported crystal structure, we considered the most active compound as a template (Fig.1(a)) for the alignment. The compound number 6 quinazolinones moiety of the bioactive molecule was used as a substructure and the rest of the molecules were aligned on it using database alignment method. The superimposition of all molecules based on minimizing root mean square deviation (RMSD) is shown in figure 1(b).

Methodology: We hereby report the models, as generated by kNN-MFA in conjunction with stepwise (SW) forward-backward variable selection methods. In the kNN-MFA method, several models were generated for the selected members of training and test sets and the corresponding best models are reported herein. VLife Molecular Design Suite (VLifeMDS), allows user to choose probe, grid size and grid interval for the generation of descriptors.

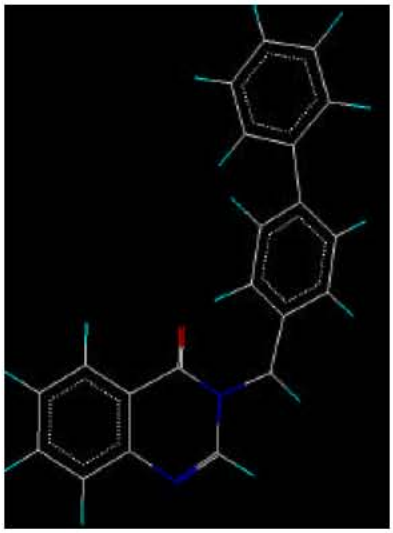


Fig. a: template molecules of the series

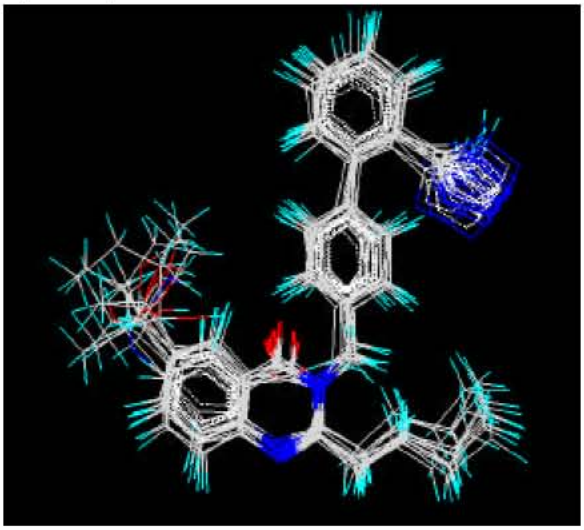


Fig. b: Aligned molecules of the series

The variable selection methods along with the corresponding parameters are allowed to be chosen and optimum models are generated by maximizing q2. k-nearest neighbor molecular field analysis (kNN-MFA) requires suitable alignment of given set of molecules. This is followed by generation of a common rectangular grid around the molecules. The steric and electrostatic interaction energies are computed at the lattice points of the grid using a methyl probe of charge +1. These interaction energy values are considered for relationship generation and utilized as descriptors to decide nearness between molecules. The term descriptor is utilized in the following discussion to indicate field values at the lattice points. This algorithm allows the construction of training sets covering descriptor space occupied by representative points. Once the training and test sets were generated, kNN methodology was applied to the descriptors generated over the grid. For calculation of field descriptor values, both electro static and steric, hydrophobic field type with cutoff values of 10.0 and 30.0 Kcal/mole 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 KNN-MFA models were generated using the variable selection methods, viz. stepwise (SW) forward- backward method and simulated annealing (SA) method.

Stepwise (SW) Method: The kNN-MFA model for all the Ang II activities was developed using stepwise forward backward method with cross correlation limit set to 0.5 and term selection criteria as q^2. The method resulted in selection of compounds no. 3, 5, 9 and 14 as test set and remaining 12 compounds as a training set. 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 Å and scaling and auto scaling, additionally the K-nearest Neighbor parameter setting was done within the range of 2-6 and prediction method was selected as distance base weighted average.

Cross-Validation Using Weighted K-Nearest Neighbor: This is done to test the internal stability and predictive ability of the QSAR models. Developed QSAR models were validated by the following procedure:

Internal and External Validation: 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 [7] (eq.1). The similarities were evaluated as the inverse of Euclidean distances between molecules (eq.2) using only the subset of descriptors corresponding to the current trial solution.

$$wi=\frac{Exp(-dj)}{\sum Exp(-dj)}$$

k - Nearest neighbour

$$\hat{y}_t=\sum Wi_{yt} \quad (1)$$

$$d_{if}=\sum_{k=1}^{m}(X_{IR}-X_{IR})^2)^{1/2} \quad (2)$$

b.) Step 1 was repeated until every molecule in the training set has been eliminated and its activity predicted once.

c.) The cross-validated r^2 (q^2) value was calculated using eq. 3, where *yi* and *yi* are the actual and predicted activities of the *i*th molecule, respectively and *y*mean is the average k-Nearest neighbor activity of all molecules in the training set. Both summations are over all molecules in the training set. Since the calculation of the pair wise molecular similarities and hence the predictions, were based upon the current trial solution, the q^2 obtained is indicative of the predictive power of the current kNN-MFA model.

$$q^2 = 1 - \frac{\sum (y_t - \hat{y}t)^2}{\sum (y_t - y_{mean})^2}$$

External Validation: The predicted r^2 (pred_r^2) value was calculated using eq. 4, where *yi* and *yi* are the actual and predicted activities of the *i*th molecule in test set, respectively and *y* mean is the average activity of all molecules in the training set. Both summations are over all molecules in the test set. The pred_r2 value is indicative of the predictive power of the current kNN-MFA model for external test set.

$$pred\_r^2 = 1 - \frac{\sum (y_t - \hat{y}t)^2}{\sum (y_t - y_{mean})^2}$$

Randomization Test: To evaluate the statistical significance of the QSAR model for an actual data set, we have employed a one-tail hypothesis testing. The robustness of the QSAR models for experimental training sets was examined by comparing these models to those derived for random data sets. Random sets were generated by rearranging biological activities of the training set molecules. The significance of the models hence obtained was derived based on calculated Z score[19].

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

Where *h* is the q^2 value calculated for the actual dataset, μ the average q2 and σ is its standard deviation calculated for various iterations using models build by different random data sets. The probability (α) of significance of randomization test is derived by comparing Z score value.

RESULTS AND DISCUSSION

All the sixteen compounds were built on workspace of molecular modelling software VLifeMDS; this method utilizes the active analogue principle that lies at the foundation of medicinal chemistry [20-23]. The 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. Selecting training and test set by spherical exclusion method, Unicolumn statics shows that the max of the test is less than max of train set and the min of the test set is greater than of train set. Which is prerequisite analysis for further QSAR study.

Model-A: pIC_{50}=2.9863-0.5528 (S_453) - 0.4392 (E_931) + 0.4875 (S_657) +0.4099 (H_229) -0.7084 $N_{traning}$ = 12, N_{test} = 4, Optimum Components = 4, DF = 19, r^2 = 0.8954, q^2 = 0.8271, F test = 83.643, r^2_se = 0.7854, q^2_se = 0.3219, pred_r^2 = 0.8413, pred_r^2se = 0.3298, Z_{Score} $Q^{\wedge 2}$ = 1.54265, Best Rand $Q^{\wedge 2}$ = 1.8742.

Model-B: pIC_{50}=1.0876-0.0180 (S_102) - 0.1808 (E_232) + 4.1474 (S_836) +0.4099 (E_931) -0.9643 $N_{traning}$ = 12, N_{test} = 4, Optimum Components = 4, DF = 19, r^2 = 0.8365, q^2 = 0.7326, F test = 64.097, r^2_se = 0.52198, q^2_se = 0. 0.2207, pred_r^2 = 0.7725, pred_r^2se = 0.7421, Z_{Score} $Q^{\wedge 2}$ = 0.95332, Best Rand $Q^{\wedge 2}$ = 2.1987.

Model-C: pIC_{50}= - 0.0876-0.1521(S_364) -10.0000 (E_564) -0.3617 (S_694) -0.2297 (E_400) -2.7258 (E_842) -1.9685 $N_{traning}$ = 12, N_{test} = 4, Optimum Components = 4, DF = 19, r^2 = 0.7194, q^2 = 0.6709, F test = 43.876, r^2_se = 0.1098, q^2_se = 0. 6538, pred_r^2 = 0.6841, pred_r^2se = 0.3984, Z_{Score} $Q^{\wedge 2}$ = 0.3673, Best Rand $Q^{\wedge 2}$ = 1.7865.

3D QSAR models were generated by kNN-MFA in conjunction with Stepwise (SW) Forward Backward selection method. From these models, two of them were having good q2 and pred_r2 values, one of which was selected having good internal and external predictivity. For this model training and test sets were selected using random selection method and the descriptors were selected using Stepwise (SW) Forward Backward selection. The QSAR models developed by kNN-MFA

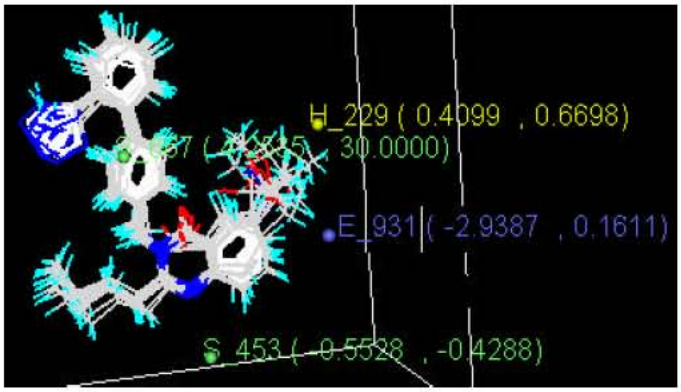


Fig. c: Stereo view of show points of all the compounds Model A

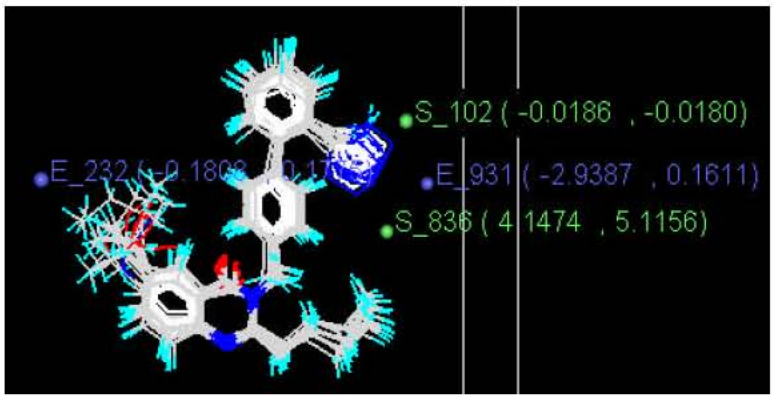


Fig. d: Stereo view of show points of all the compounds Model B

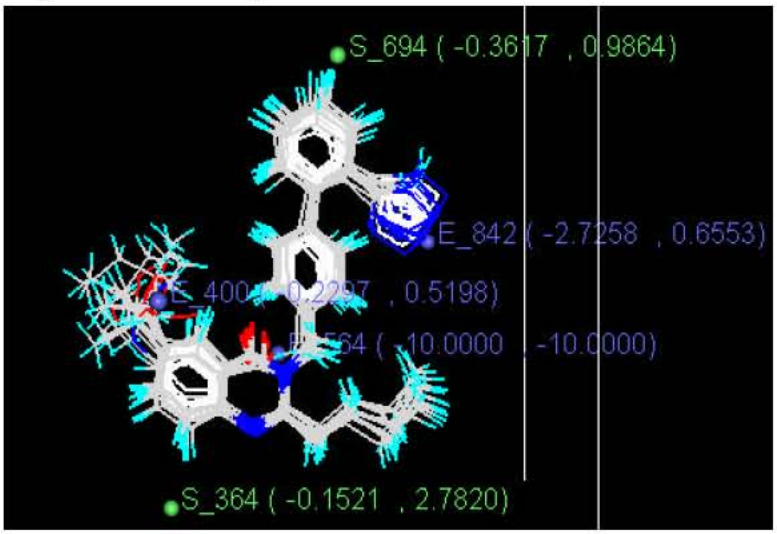


Fig. e: Stereo view of show points of all the compounds Model C

include both the electro static and steric, hydrophobic field descriptors along with their range to indicate there importance for interaction in molecular field. Analysis of model suggested that both steric and electrostatic descriptors are important for interaction. Model-A (Fig.c) the template based alignment shows a q^2 (cross validated r^2) of 0.8271 with four descriptors namely S_453, E_931, S_657 and H_229. A non-cross-validated *r2* of 0.8954, *F* value of 83.643 and number nearest neighbors *k* of 4 were observed with this model. i.e all the values are proved statistically significant. The steric and electrostatic hydrophobic contributions were 55 and 30 and 15 %,

respectively and exhibited good external prediction with r^2 *pred* of 0.8413. Statistical significance of the model indicated by *Z score* value of 1.54265 and α of >0.0001.Model-B (Fig.d) the kNN-MFA model generated from template based alignment showed *q2* (cross validated *r2*) of 0.7326 with four descriptors namely S_102, E_232, S_836 and E_931. A non-cross validated *r2* of 0.8365, *F* value of 64.097 and number nearest neighbors *k* of 4 were observed with this model. The steric and electrostatic, hydrophobic contributions were 40,25 and 35 %, respectively and exhibited good external prediction with *r2 pred* of 0.68. Statistical significance of the model indicated by *Z score* value of 2.66 and α of >0.001.Model-C(fig.e), the kNN-MFA model generated from template based alignment showed *q2* (cross validated *r2*) of 0.6709 with four descriptors namely S_364, E_564, S_694 and E_400. A non-cross validated *r2* of 0.7194, *F* value of 43.876 and number nearest neighbors *k* of 4 were observed with this model. The steric and electrostatic, hydrophobic contributions were 40,25 and 35 %, respectively and exhibited good external prediction with *r2 pred* of = 0.6841. Statistical significance of the model indicated by *Z score* value of 0.3673 and α of >0.001. Most significant models were generated by SW variable selection method. The value of cross validated correlation coefficient which is assumes to be a measure of goodness of internal predictivity of the model. The external predictive power i.e. the value of pred_r^2 for a model is valuable in the evaluation of a QSAR model. A comparison of values of pred_r^2 in all the models and considering the above fact the model SW kNN-MFA was found to be q^2=0.8271 and pred_r^2 = 0.8413 which explains 82% internal and 84 % external predictive power of the model respectively. A closer view to the selected descriptors suggested that descriptor S_453, E_931, S_657 and H_229 were included in SW kNN-MFA model and thus play a significance role in the structure activity relationship. The statistically most significant, SW kNN-MFA model used electrostatic and steric field descriptor along with its k nearest neighbors (k=4) to evaluate the activity of a new molecule. Model of the kNN-MFA which shows the relative position and ranges of the corresponding important electrostatic and steric fields in model provides guidelines for new molecule design. Negative rang indicate that negative electrostatic potential and steric potential are favorable for increase in the activity and hence more electronegative substituents group is preferred in that region. Positive electro potential and steric potential are favorable for increase in activity and hence a less electronegative group is preferred in this region. The selected model has shown contribution of S_453, S_657, steric descriptors in activity. The decrease in positive potential of S_657 descriptor indicates that less bulky substituent on (R_2) position decreases Ang II activity. The increase in positive value of S_453, E_931 and H_229 shows that aromatic ring (R_1, R_2,R_3) is important for activity and it can be replaced with large bulky ring substituent. Negative range of steric field indicates that less bulky substituent would be favourable for the activity. Positive range of electronic field 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.

Table 3: Comparative observed and predicted activities (LOO) of QSAR models

Observed activity	Predict activity-A	Predict activity-B	Predictactivity-C
1.00	1.16	1.09	1.28
0.95	0.71	0.67	0.81
1.08	0.89	0.78	0.94
0.95	0.66	0.72	0.81
1.17	1.33	1.26	1.01
1.14	0.89	0.90	0.91
3.00	3.21	3.18	2.79
3.00	3.04	2.96	2.87
1.25	1.10	0.98	0.92
0.84	0.62	0.58	0.70
0.69	0.85	0.91	0.48
0.78	0.60	0.89	1.03
0.95	1.19	0.74	0.69
0.78	0.57	0.63	0.95
2.11	2.29	1.96	1.90
2.11	2.01	2.26	2.33

With the view of all above also based on the predictive Table 3 ability of three kNN-MFA models, analysis A, the model generated with template based alignment and four components exhibits good predictive. Model B the external predictive power i.e. the value of pred_r^2 for a model is valuable in the evaluation of a QSAR model. A comparison of values of pred_r^2 in all the models and considering the above fact the model SW kNN-MFA was found to be q^2=0.7326 and pred_r^2 = 0.7725 which explains 73% internal and 77 % external predictive power of the model respectively. Model of the kNN-MFA which shows the relative position and ranges of the corresponding important electrostatic and steric fields in model provides guidelines for new molecule design. Negative range indicates that negative electrostatic potential and steric potential are favorable for increase in the activity and hence more electronegative substituents group is preferred in that region. Positive electrostatic potential and steric potential are favorable for increase in activity and hence a less electronegative group is preferred in this region.

CONCLUSIONS

In conclusion, a novel three-dimensional QSAR approach has been developed based on the principles of the k-nearest neighbor method. The method employs different variable selection procedures with stepwise forward, for the three data sets reported in this study, it can be seen that SW kNN-MFA methods generate better models with higher prediction accuracy procedure. The location and range of function values at the field points selected by the models provide clues for the design of new molecules.The 3D-QSAR study of 16 substituted-4(3H) Quinazolinones derivatives which Ang II was carried out using kNN-MFA method with the template base methods. We find that the template based alignment shows this superimposition produced a good external prediction. The kNN-MFA model obtained from atom based alignment having better r^2 values than template based alignment. This indicates that all ligands have to be superimposed by the template structure used for alignment. Also it showed good correlation with biological and predictive ability. Steric and electrostatic, hydrophobic fields were found important for antihypertensive activity as exemplified by the higher predictive power of the kNN-MFA model. The results obtained from the 3D-QSAR models were found to accurately predict structurally diverse test set of compounds and to yield reliable clues for further optimization of substituted-4(3H) Quinazolinones derivatives in the data set. 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 neighbor set. The location and field values of these points can be used for the design of novel and better molecules.

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