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Research Article

Development of 2D and 3D Quantitative Structure Activity Relationship Models of Thiazole Derivatives for Antimicrobial Activity

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ABSTRACT

A series of 20 molecules of Aryl Thiazole derivatives reported in literature Khan M S *et al* (2009) were used for development of 2D and 3D quantitative structure activity relationship (QSAR) models. The data set of 20 molecules were divided into training and test set in the ratio of 70:30, The biological activity was converted to logarithmic scale (pIC_{50}) in mathematical operation mode of the software. The statistically significant 2D-QSAR models for G+ inhibition activity are r^2 =0.9521 and q^2 = 0.8619 and 3D QSAR results for internal (q^2 = 0.8283,) and external (predictive r^2 = 0.4868,) validation criteria. Thus, 3D QSAR models showed that electrostatic effects at the area of [E_685 (-10.00-0.10.00)+E_460(-0.4530-0.273)+E_531(-0.6212-0.2506)]dominantly determine the binding affinities. 2D QSAR studies revealed that T_C_C_4 descriptors were major contributing descriptor in case of G+ inhibition activity. 3D QSAR Methods were performed using kNN-MFA method. The results derived may be useful in further designing novel more potent agents.

Introduction

Thiazole and its derivatives have been associated with a wide variety of biological and pharmacological activity.[1,2] The 2- aminothiazole-ring system has found application in the drug development for the treatment of HIV infection, allergy, hypertension and inflammation.[3] Thiazole derivatives are also well known for their bactericidal, fungicidal and anthelmintic properties.[4] Further many azetidinone and thiazolidinone derivatives were also reported for their antimicrobial agents.[5] In recent years, noteworthy advancement has been made by computational chemistry which led new challenges to drug discovery.

Quantitative structure activity relationship (QSAR) which has become reputable tool for establishing quantitative relationship between biological activity and physicochemical properties of the compounds in a series using various statistical methods (linear regression and non- linear regression analysis) and it helps to calculate the biological activities of newly designed analogues contributing to the drug discovery process.[6] The core idea of the present study is the search for novel aryl thiazole analogues that would show a promise to become useful as inhibitors of G+ bacteria. A series of aryl thiazole analogues which were reported[7] are chosen for QSAR study in order to establish quantitative relationship between physiochemical properties and biological activities of the compounds using QSARpro software (Vlife Science).[8]

The purpose of the present study is to investigate the physico-chemical parameters responsible for the G+ inhibition effect of aryl thiazole derivatives and designing of novel substituted aryl thiazole derivatives with potent protective activity. In the present investigation, three

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widely used techniques, viz. stepwise forward variable selection method, genetic algorithm and simulated annealing have been applied for descriptor optimization and multiple linear regression analysis, principal component regression and partial least square has been applied for two and three-dimensional 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 protecting effect of novel of aryl thiazole molecules. The data set were divided into training and test set as in 70:30 ratio

Traditional QSAR does not directly take into account the three- dimensional nature of molecules. However, three- dimensional QSAR uses steric and electrostatic parameters in an attempt to define the three- dimensional shape, and electrostatic fields of a molecule responsible for binding to produce QSAR type equations for predicting the activity of potential drug candidates.[9]

In 3D QSAR the 3D properties of a molecule are considered as a whole rather than by considering individual substituent or moieties. The philosophy of 3D QSAR revolves around the assumptions that the most important features about a molecule are its overall size and shape, and its electronic properties (electronic field). Comparative molecular field analysis (CoMFA) is an important method of 3D QSAR.[10] This is based on the assumption that drug–receptor interactions are non-covalent and that changes in the steric and/or electrostatic fields of the drug molecules.[11]

3D QSAR like traditional QSAR uses a group of compounds, the training set, with either similar structures or having a common pharmacophore and same type of activities but different potencies in an investigation. A 3D QSAR investigation is thus started by selecting one member of the training set as a reference compound and identifying its pharmacophore. The three-dimensional structure of a reference molecule is locked into a rectangular three- dimensional lattice of so- called grid points that are usually set at a finite distance apart, typically 2 angstrom units (0.2 mm), in the x, y, and z directions. Each grid point is located by a three- or four-digit number. A suitable molecular mechanical probe, such as a sp^3- hybridized carbon atom with a charge of +1, is placed in turn at each of these grid points. Three probs in common use are a proton (H^+), a methyl carbonium ion ($^+CH_3$) and water (H_2O). H^+ is used for electrostatic, $^+CH_3$ for steric and H_2O for hydrophobic interactions.

The next stage of the analysis is to align the other molecules of the training set in the lattice and measure their steric and electrostatic field. Aligning the pharmacophore of the set molecules with that of reference molecule usually gives good analysis results.

Similarly, an alignment based on matching the positions of the common sections of the structure of the set molecules, such as steroidal ring system, gives good analysis results. The data from all the calculations are converted into a QSAR equation using statistical methods.

A series of aryl thiazole derivatives which were reported [12] are chosen for QSAR study to establish quantitative relationship between physiochemical properties and biological activities of the compounds using MDS software (Vlife Science).[13]

The rational reason for doing QSAR is that the by doing QSAR we can remove the elements of risk from the synthesized molecules, and the newly designed molecules may have the better activities and very less chances of side effects. By doing QSAR we can enhance the chemical activity of the said lead compound and remove the unwanted things which we don't required.

For the selection of given series first we selected the 20 molecules which was already synthesized and available in paper[14] having the sigmoidal activity graph and molecules are having molecules weight not more than 4000 Dalton and we can distribute it for training and test set in 70:30 ratio so it is very good to use said compound for the 2D and 3D QSAR.

Materials and Methods

All molecular modeling studies (2D and 3D) were performed using the Molecular Design Suite (VLife MDS software package, version 4.6; from VLife Sciences, Pune, India), on a Dell computer with a Core I -3processor and a Windows 7 operating system. Structures were sketched using the 2D draw application and converted to 3D structures (Table 1).

Biological Data

The G+ inhibition was taken from the reported work. The antibacterial activity of thiazole derivatives was studied comparatively with that of standard antibiotics Ciprofloxacin by cup plate method using gram positive organisms *Staphylococcus epidermatitis.* Medium A is prepared as per Indian pharmacopoeia.

Method of Testing

Cup Plate Method

This method depends on the diffusion of an antibiotic from a cavity through the solidified agar layer in a Petri dish to an extent such that growth of the added microorganism is prevented entirely in a circular area or zone around the cavity contain solutions of antibiotic.

A previously liquefied medium was inoculated appropriated to the assay with the requisite quantity of the suspension of the microorganisms between 40 to 50°C and the inoculated medium was poured into Petri dish to give a depth of 3–4 mm. ensured that the layers of medium were uniform in thickness by placing the dishes on a leveled surface

The dishes thus prepared were stored in a manner so as to ensure that no significant growth or death of the test organisms occurs, before the dishes were used and the surface or the agar layer was dry at the time of use. With the help of a sterile cork borer, two cups of each 6mm diameter were punched and scooped out the set agar in each Petri dish (two cups were numbered for the particular compound and standards). Using sterile pipettes, the standard and the sample solutions (0.1-mL) of known concentration were fed into the borer cups. The order of the solutions was as follows.

Cup-1: Standard (Ciprofloxacin)

Cup-2: Solvent control (DMF)

Cup-3: Test compound

The dishes were left standing for one hour at room temperature as a period of pre incubation diffusion to minimize the effects of variation in time in time among the application of different solutions. These were then incubated for 24 hours at 37°C. The zone of inhibition developed, if any, was then accurately and recorded. Each zone of inhibition recorded was average of three measurements. Zone of inhibition for DMF was done separately. The data were taken from the previously published article.[15].

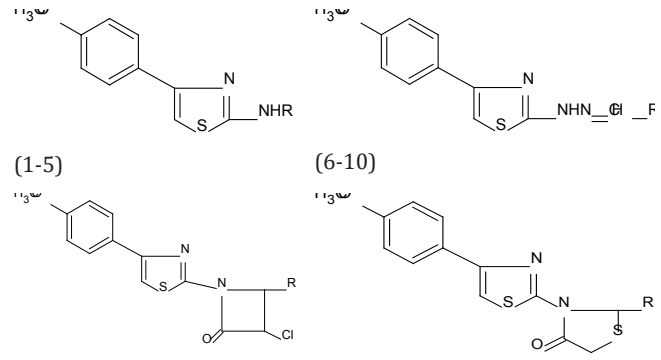
The total set of compounds were divided into a training set for generating 2D and 3D QSAR models and a test set for validating the quality of the models. Selection of the training set and test set molecules was done based on structural diversity and a wide range of activity such that the test-set molecules represent a range of biological activity similar to that of the training set; thus, the test set is truly representative of the training set. The biological activity values [IC_{50} (μM)] reported in micro molar units were converted to their negative logarithmic scale and subsequently used as the dependent variable for the QSAR analysis. The values of IC_{50} along with the structure of the compounds in the series are listed in Table 1.

Result of multiple linear regression (MLR) analysis using random data selection and manual data selection methods is shown in Table 2 and 3 respectively for all two activities.

Molecular Modeling for 2D QSAR

In 2D QSAR analysis, significant methods Multiple linear regression, principal component regression and partial least square were applied to generate the 2D-QSAR model. The 2D structures were converted to 3D structures by sending them to MDS software. Each compound was energy minimized and batch optimized by using Merck Molecular Force Field and charges followed by Austin Model-1. Hamiltonian method was available in MOPAC module with the convergence criterion 0.001 kcal/mol A° fixing Root Mean Square Gradients (RMS) to 0.001 kcal/mol A°. 2D descriptors (physicochemical and alignment independent) were calculated for the optimized compounds on QSAR plus work sheet. The invariable descriptors (the descriptors that are constant for all the molecules) were removed, as they do not contribute to QSAR. Most stable structure for each compound was generated after energy minimization and used for calculating various physicochemical descriptors like thermodynamic, steric and electronic. The energy-minimized geometry was used for the calculation of the various 2D descriptors (Individual, Chi, ChiV, Path count, Chi Chain, ChiV Chain, Chain path count, Cluster,

Table 1: Structures of aryl thiazole derivatives with activity[15]



(1-5) (6-10)

(11-15) (16-20)

		Activity	
Compound	*R_1*	*G+activity*	*Log_NO*
1	H	10	1
2	C_6H_5	17	1.2304
3	$C_6H_4CH_3(2)$	15	1.176
4	$C_6H_4Cl(4)$	22	1.3424
5	$C_6H_4F(4)$	21	1.3222
6	C_6H_5	16	1.2041
7	$C_6H_4OH(2)$	11	1.0413
8	$C_6H_4OH(4)$	21	1.3222
9	$C_6H_4OCH_3(4)$	16	1.2041
10	$C_6H_4Cl(4)$	22	1.3424
11	C6H5	11	1.0413
12	C6H4OH(2)	21	1.3222
13	C6H4OH(4)	21	1.3222
14	C6H4OCH3(4)	16	1.2041
15	C6H4Cl(4)	17	1.2304
16	C_6H_5	11	1.0413
17	$C_6H_4OH(2)$	22	1.3424
18	$C_6H_4OH(4)$	18	1.2552
19	$C_6H_4OCH_3(4)$	22	1.3424
20	$C_6H_4Cl(4)$	21	1.3222

* Inhibition of G+

Table 2: Grid Settings for aryl thiazole derivatives

Axis	*From*	*To*	*Interval*
X	-3.28565	21.6938	2.000
Y	-3.50321	13.8944	2.000
Z	-8.20132	7.52432	2.000

Path cluster, Kappa, Element Count, Estate number, Estate contribution, Semi-empirical, Hydrophilic– hydrophobic, Polar surface area and Alignment independent) and was considered as independent variables in the present study.

QSAR analysis was performed after removal of all the invariable columns, as they do not contribute to the QSAR. The optimal test and training data set were generated using the manual as well as random data selection method. Sphere exclusion method was also adopted for division of training and test set. Sphere exclusion method is used for creating training and test set from the data. This is a rational selection method which takes into consideration both biological and chemical space for division of data set. Dissimilarity value provides handle to vary train/test set size. It needs to be adjusted by trial and error until a desired division of training and test set is achieved. As a rule, increase in dissimilarity value will lead to increase in number of molecules in the test set. All 23 molecules were subjected to regression analysis using multiple linear regression analysis, as model building methods coupled with stepwise forward backward variable selection method. Regression analysis was carried out for treatment of drug abuse disorders and the best model was cross-validated. Best two dimensional QSAR results obtained by multiple linear regression analysis, Partial Least Squares and Principal Component Regression are obtained shown in Table 2, and 3 respectively.

Molecular Modeling for 3D QSAR

In 3D QSAR All molecules were aligned by using template-based method and aligned molecules were used for 3D QSAR taking consideration on RMS gradient between 0.1 to 0.5.

Significant method was used like kNN(nearest neighbor)[16] and neural network methods both methods were combined with the stepwise variable selection forward backward method taking consideration of data in 70:30 ratio of training and test set. The subjected molecules were used for 3D QSAR the Steric and electrostatic parameters used with distance dependent function with charge of Gasteiger marsili of constant 1 and cut offs of electrostatic 10 kcal/mole and steric 30kcal/mole were used. Grid selection for those molecules is in Table 2

Development and validation of QSAR Models were generated by using significant statistical methods, namely, MLR and k-nearestneighbour molecular field analysis (kNN-MF) method. The following statistical parameters were considered to compare the generated QSAR models: correlation coefficient (r), squared correlation coefficient (r^2), i.e., q^2, predicted r^2 (pred_r^2), and Fischer's value (F).[17]

The leave-one-out (LOO) method indicated the value of q^2 (cross-validated explained variance), which is a measure of the internal predictive ability of the model and pred_r^2 which is a measure of the external predictive ability of the model.[18]

Result and Discussion

The selection of the best model is based on the values of r^2 (squared correlation coefficient), q^2 (cross-validated correlation coefficient), pred_r^2 (predicted correlation coefficient for the external test set), F (Fisher ratio) value. High values of the F-test indicated that the model was statistically significant. r^2se, q^2se and pred_r^2se are the standard errors terms for r^2, q^2 and pred_r^2 respectively. The statistically significant 2D-QSAR model is shown as follows.

Interpretation of the Model -1for G+

Model-(Test set: 1, 15, 2 and 18)

***p*IC$_{50}$ (column)** = -0.1541(T_C_C_4) +0.2334 (K1alpha) -0.0044 (SsOHCount) +0.0802(T_N_S_2)-0.0099(T_O_O_6)-0.1832(T_T_N_7)+0.2727(T_N_O_6) -0.1815 (H-donor Count)+0.4564 (chi4chain)+0.0462(T_C_F_4)+0.00.

Statistics

[n= 16; Degree of freedom= 05; r^2 =0.9521; q^2=0.8619; F test=9.9286; r^2se=0.0440; q^2se= 0.0747; pred_r^2= 0.6932; pred_r^2se = 0.0780]

From equation, model 1 explains 95.21% (r^2 =0.9521) of the total variance in the training set as well as it has internal (q^2) and external (pred_r^2) predictive ability of 86.19 % and 69.32 % respectively. The F test shows the statistical significance of 99.99 % of the model which means that probability of failure of the model is 1 in 10000. In addition, the randomization test shows confidence of 99.9999 (Alpha Rand Pred R^2 = 0.00000) that the generated model is not random and hence chosen as the QSAR model. The F-test=14.63 which is greater than the tabulated value 1.54 (2). From QSAR, model 1 indicated-

- Negative coefficient value of T_C_C_4 [This is the count of number of any single or double bonded carbon separated by other carbon by four bonds] on the inhibitory activity indicated that lower value leads to better inhibitory activity whereas higher value leads to decrease inhibitory activity.
- Positive coefficient value of K1alpha [This This descriptor signifies first alpha modified shape index: s (s-1)2/m2

Table 3: Results of MLR analysis using random data selection method for G+ activity of derivatives

Sr. no.	*r^2*	*q^2*	*r^2se*	*q^2se*	*F test*	*Predr^2*	*Predr^{2}se*	*n*	*DOF*
1	o.9521	0.8619	0.0440	0.0747	9.928	0.6932	0.0780	16	5
2	0.9776	0.8744	0.0484	0.1147	4.3731	0.4509	0.1318	12	1
3	0.9957	0.9040	0.037	0.1120	23.21	0.0.4047	0.1043	12	1

where s = n + a [19]. on the inhibitory activity indicated that higher value leads to better inhibitory activity whereas lower value leads to decrease inhibitory activity.

- Negative coefficient value of SsOH Count [This descriptor defines the total number of –OH group connected with one single bond.] on the inhibitory activity indicated that lower value leads to better inhibitory activity whereas higher value leads to decrease inhibitory activity.
- Positive coefficient value of T_N_S_2 [This is the count of number of Nitrogen atoms (single double or triple bonded) separated from any other Sulfur atom (single double or triple bonded) by two bonds in a molecule]. On the biological activity indicated that higher values lead to good inhibitory activity while lower value leads to reduced inhibitory activity.
- Negative coefficient value of T_O_O_6 [This is the count of number of oxygen atoms (single double or triple bonded) separated from any other oxygen atom (single double or triple bonded) by six bonds in a molecule]. On the inhibitory activity indicated that lower value leads to better inhibitory activity whereas higher value leads to decrease inhibitory activity.
- Negative coefficient value of T_T_N_7 [This is the count of number of single double or triple bonded atoms separated from any Nitrogen atom (single double or triple bonded) by seven bonds in a molecule.] on the inhibitory activity indicated that lower value leads to better inhibitory activity whereas higher value leads to decrease inhibitory activity.
- Positive coefficient value of T_N_O_6 [This is the count of number of Nitrogen atoms (single double or triple bonded) separated from any oxygen atom (single double or triple bonded) by six bonds in a molecule]. On the biological activity indicated that higher values lead to good inhibitory activity while lower value leads to reduced inhibitory activity.
- Negative coefficient value of H-donor count [Number of hydrogen bond donor atoms] on the inhibitory activity indicated that lower value leads to better inhibitory activity whereas higher value leads to decrease inhibitory activity.
- Positive coefficient value of chi4chain [This descriptor signifies a retention index for four membered ring]. On the biological activity indicated that higher values lead to good inhibitory activity while lower value leads to reduced inhibitory activity.
- Positive coefficient value of T_C_F_4 [This is the count of number of carbon atoms (single double or triple bonded) separated from any flurine atom (single double or triple bonded) by four bonds in a molecule]. On the biological activity indicated that higher values lead to good inhibitory activity while lower value leads to reduced inhibitory activity.

Contribution chart data fitness plot and activity of training and test set for model 4 is represented in Fig. 1 to 4.

3D QSAR for Thiazole Derivatives

kNN-MFA samples the steric and electrostatic fields surrounding a set of ligands and constructs 3D-QSAR models by correlating these 3D fields with the corresponding biological activities. Molecular alignment was used to visualize the structural diversity in the given set of molecules. The template structure Thiazole derivatives was used for alignment by considering the common elements of the series as shown in Figs. 5 and 6.

3D QSAR for G+

Model-1 (Test set: 10, 17, 19, 20, 4 and 9)

pIC_{50}= E_685 (-10.00-0.10.00)+E_460(-0.4530-0.273)+E_531(-0.6212-0.2506)

Statistics: [kNN= 2; n = 14; DOF= 10; q^2= 0.8283; q^2_se = 0.0488; pred_r^2 = 0.4868; pred_r^2se = 0.1038] (Table 4).

The model 1 explains values of k (2), q^2 (0.8283), pred_r^2 (0.4868), q^2_se (0.0488), and pred_r^2 se (0.1038) prove that QSAR equation so obtained is statistically significant and shows the predictive power of the model is 82.83% (internal validation).

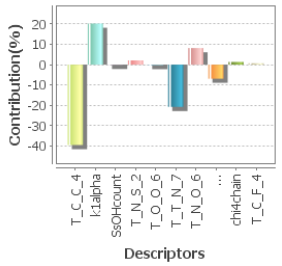


Fig. 1: Contribution Plot

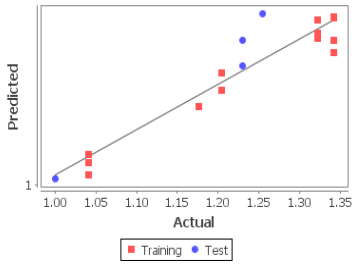


Fig. 2: Fitness plot

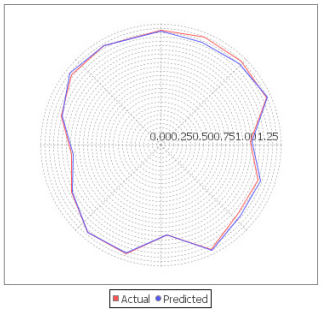


Fig. 3: Training Set

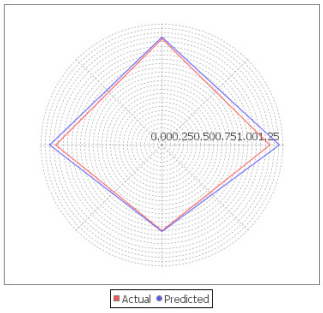


Fig. 4: Test Set

Fig. 5: Template molecule

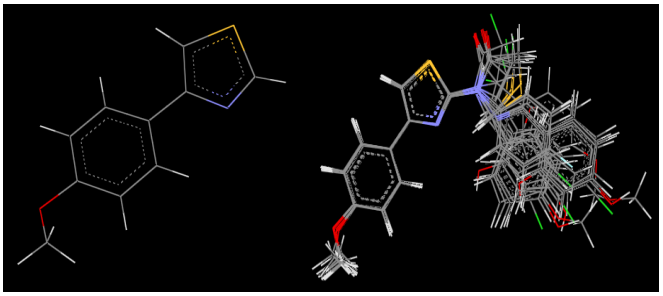


Fig. 6: Stereo view of aligned molecules

Table 4: Statistical evaluation of 3D-QSAR models of Thiazole derivatives

Trials	*kNN*	*n*	*DOF*	q^2	q^2_se	pred_r^2	pred_r^2se
1(Model-1)	2	14	10	0.8283	0.0488	0.4868	0.1038
2(Model-2)	2	14	10	0.6784	0.714	0.4656	0.0834
3(Model-3)	2	14	10	0.5147	0.0182	0.2182	0.0813

Table 5: Actual vs. predicted activity of 3', 4', 5'trimethoxy chalcone derivatives

Molecules	*G+ actual*	*G+ 2D predicted*	*G+ 3D predicted*
1	1	1.01302	1.001947
2	1.2304	1.251788	1.267038
3	1.176	1.166391	1.176006
4	1.3424	1.356165	1.3222
5	1.3222	1.321994	1.3222
6	1.2041	1.199763	1.256188
7	1.0413	1.045982	1.0413
8	1.3222	1.318659	1.270112
9	1.2041	1.238089	1.142076
10	1.3424	1.305994	1.3222
11	1.0413	1.021151	1.0413
12	1.3222	1.310513	1.307486
13	1.3222	1.320445	1.321979
14	1.2041	1.237038	1.204209
15	1.2304	1.306835	1.230621
16	1.0413	1.063942	1.0413
17	1.3424	1.353353	1.163981
18	1.2552	1.363285	1.255091
19	1.3424	1.279925	1.222574
20	1.3222	1.349691	1.267358

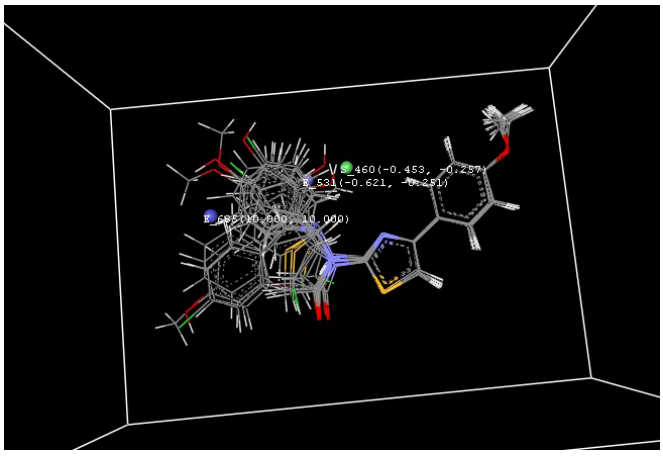


Fig. 7: Plot of contribution chart

Table 5 represents the predicted inhibitory activity by the model-1 for training and test set.

The data fitness plot for model 1 is shown in Fig. 7. The plot of observed vs. predicted activity Figs. 8 to 10 provides

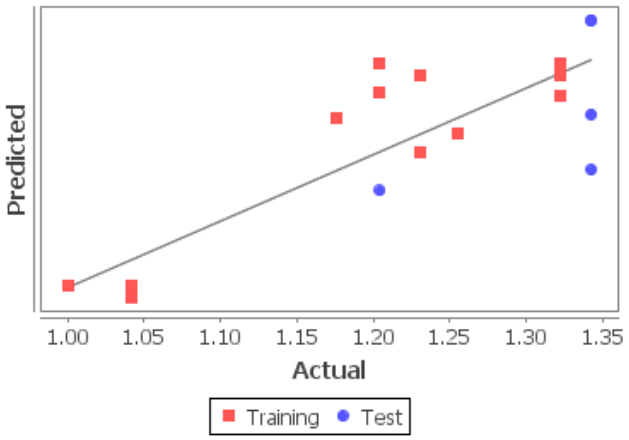


Fig. 8: Data fitness plot

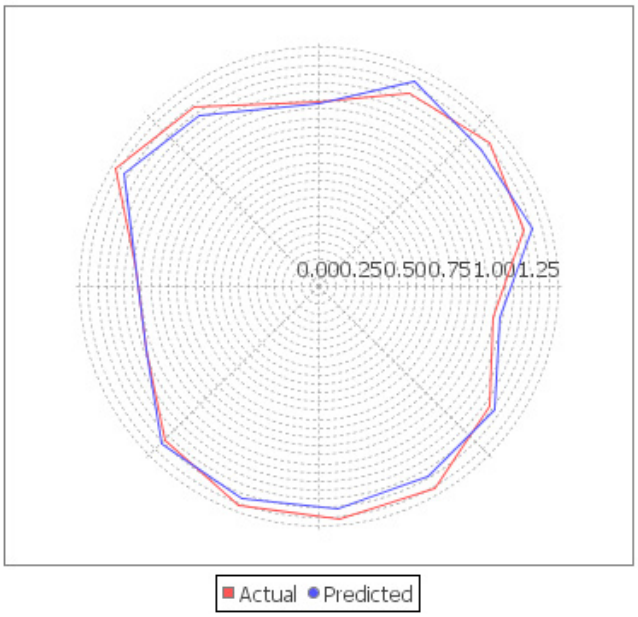


Fig. 9: Training Set

an idea about how well the model was trained and how well it predicts the activity of the external test set.

Electrostatic field, E_685 (10.00-0.10.00) Positive Electrostatic potential is favorable for increase in the activity and hence bulkier substituent group is preferred in that region.

Electrostatic field, E_460 (-0.4530-0.273) negative electrostatic potential is favorable for increase in the activity and hence less bulky substituent group is preferred in that region.

Electrostatic field, E_531(-0.6212-0.2506) negative electrostatic potential is favorable for increase in the

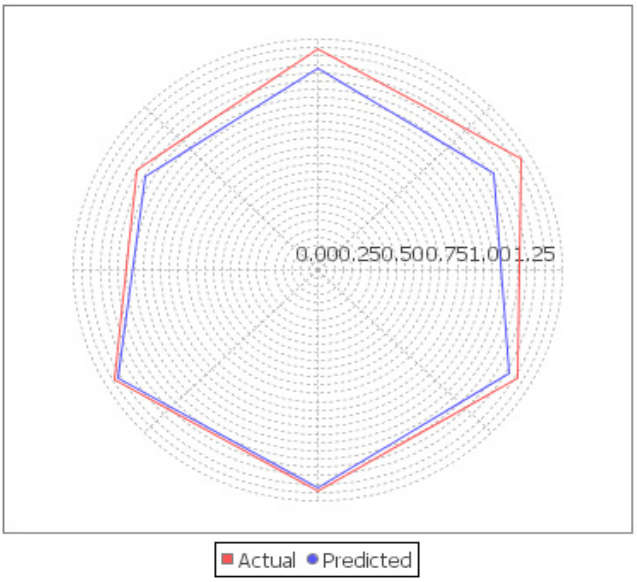


Fig. 10: Test Set

activity and hence less bulky substituent group is preferred in that region.

Design and Activity Prediction of Newer Derivatives

From the best models obtained, some newer compounds were designed which having the better activity than the reported one. The structures were not reported earlier anywhere is confirmed by chem. Spider.

Conclusions

In the present investigation, all proposed QSAR models were statistically significant, thus, from above QSAR investigations it could be concluded that 2D/3D descriptors properties of substituted 3'aryl thiazole derivatives are mainly involved in treatment of G+ inhibitor. The good correlation between experimental and predicted biological activity for compounds in the test set further highlights the reliability of the constructed QSAR model. The requirements for the more potent biological activity are explored with 2D, 3D and group based QSAR studies. The 2D technique indicates the importance of T_C_C_4, K1alpha, SsOH Count, T_N_S_2, T_O_O_6, T_T_N_7, T_N_O_6, H-donor Count, chi4chain, T_C_F_4 G+ inhibition activity of the compounds. The 3D QSAR analysis makes it possible to relate chemical structures of ligands and their binding affinity with respect to different bio targets by using the kNN-MFA techniques. Thus, it provides a direct view of factors expressed in terms of molecular fields (electrostatic, steric) affecting the binding affinity. This in turn could give the reasonably good prediction of binding affinity. The location and range of function values at the field points selected by the models provide clues for the design of new molecules. Hence, this method is expected to provide a good alternative for the drug design.

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