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Three dimensional quantitative structure analysis substituted 1,3-diaryl propenone derivatives as antimalarial activity

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ABSTRACT

Molecular modeling analysis performed by k nearest neighbor molecular field analysis (kNN MFA) to recognize the necessary structural requirements of 1,3-diaryl propenone derivatives in 3D chemical space for adjusting modulation of the antimalarial activity. In study 14 compounds were selected randomly, using sphere exclusion (SE) algorithm and random selection method struture divided into training and test set. kNN-MFA methodology with stepwise (SW), simulated annealing (SA) and genetic algorithm (GA) was used for building the QSAR models. Predictive models were generated with SW-kNN MFA. The most significant model 1 is having internal predictivity 64.24% (q2 = 64.24) and external predictivity 61.57 % (pred_r2 = 0.61.57). Model showed that steric (S_584), and electrostatic (E-295) interactions play important role in determining DPP IV inhibitory activity.

Keyword: Antimalarial agent, 1,3-diaryl propenone derivatives, simulated annealing, genetic algorithm, predictivity

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INTRODUCTION

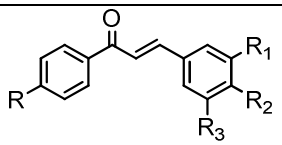
In spite of worldwide efforts to combat malaria, it still kills approximately one million people, mostly children, each year [1]. The World Malaria Report 2012 highlighted the progress made towards the global malarial targets set for 2015 and described current challenges for global malaria control and elimination [2]. Malaria is caused by different species of *plasmodium*, namely *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae* and is transmitted by female mosquitoes belonging to the genus Anopheles to humans. Endemic disease indicates that *P. falciparum* and *P. vivax* were most dangerous and spreads 95% of malaria infections in the world wide . In humans it is spread by sporozoa of the genus *plasmodium*, characterized by episodic fever, anemia and enlargement of the liver and spleen [10]. There is no fully effective prophylactic vaccine against malaria to date [3,4], and the major problem in the chemotherapy of malaria is the development of resistance of the Plasmodium falciparum parasites to many of the standard quinoline antimalarial drugs such as chloroquine [5]. The discovery of chloroquine resistance drugs has opened a new era in malarial chemotherapy which are highly active against both chloroquine-sensitive and chloroquine resistant strains of P. falciparum [6]. The chloroquine resistant drugs and artemisinin combination therapy is currently the best option available for the chemotherapy of malaria [7]. Ligand-based approaches such as three-dimensional quantitative structure–activity relationship (3D-QSAR) studies have been very useful in identifying the essential structural requirements for biological activity of compounds where the 3D structure of the exact target is unknown [8,9]. Therefore, considering the importance of 1,3-diaryl propenone and its analogues as a potent class of antimalarial drugs effective against the multidrug-resistant *P. falciparum* strains, and the unavailability of the exact target for this class of molecule [10], molecular modeling and [11] quantitative pharmacophore model utilizing this class of molecules [12]. V-life based models are computationally intensive and

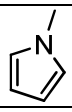
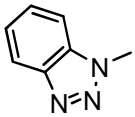
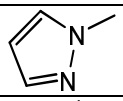
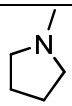
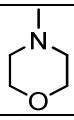
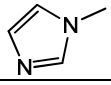
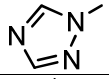
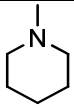
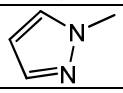
generate the QSAR equations [13]; they give the minimum essential structural requirements for activity in terms of selected regions. The successful application of computational approaches to understand the effect of contrasting structural requirements in 3D chemical space has been reported by many research groups in the recent past [14,15], which should not only provide the information about favourable regions, but also provide information about unfavourable regions in defining potency.

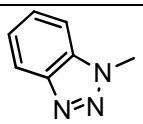
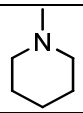
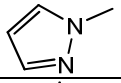
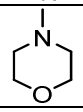
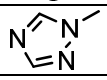
MATERIALS AND METHODS

Data Set: The QSAR studies were performed using three series of 1,3-diaryl propenone derivatives reported in literature [20]. The homogeneity of the biological assays (pIC_{50}= activity ranges from 4.909 to 5.818 µM) on Plasmodium falciparum is one of the important aspects in a QSAR study, therefore the dataset was collected from same pharmacological testing protocol. It has been suggested that generated models should be tested on a sufficiently test set to establish a statistically meaningful and reliable QSAR model; therefore, the molecules were randomly divided into a training set and a test set compounds in such a way that both sets cover the structural diversity, chemical prototypes and the complete range of antimalarial activity (Table 1). The pharmacological activity expressed in IC_{50} µM was converted into -log IC_{50} and used as dependent variable in the QSAR study.

Table 1: General structure of the compounds of substituted 1,3-diaryl propenone derivatives and their biological activities (data set of 14 molecules)

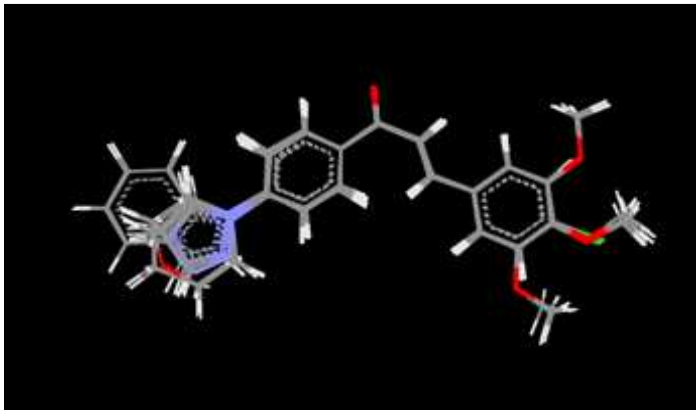


Compound	R	R1	R2	R3	IC_{50} (µM)	pIC_{50}
1.		H	Cl	H	2.93	5.533
2.		H	Cl	H	2.5	5.602
3.		H	Cl	H	7.76	5.11
4.		H	Cl	H	6.01	5.221
5.		H	Cl	H	9.1	5.041
6.		H	Cl	H	8.26	5.083
7.		H	Cl	H	1.52	5.818
8.		H	Cl	H	5.15	5.288
9.		H	OMe	H	12.33	4.909

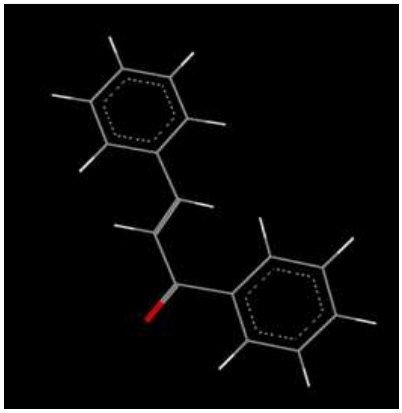
10.		H	OMe	H	6.8	5.167
11.		OMe	OMe	OMe	7.16	5.145
12.		OMe	OMe	OMe	6.0	5.222
13.		OMe	OMe	OMe	4.6	5.337
14.		OMe	OMe	OMe	8.03	5.095

Molecular Modeling Study: Molecular modeling and kNN-MFA study was performed on the software Molecular Design Suite (MDS) 4.1.19092011 [21]. The selected dataset were aligned by template based method using most active molecule 14 as a reference molecule (1) and structure (2) as a template shown in figure 1. The alignment of all the molecules on the template is shown in figure 1 as a reference aligned molecule.

Figure 1: Template structure (1) and reference aligned Molecule structure (2)



1



2

Once the molecules are aligned, a molecular field is computed on a grid of points in space around the molecule. This field provides a description of how each molecule will tend to bind in the active site. Descriptors selected were steric, electrostatic and hydrophobic interaction energies of them computed at the lattice points of the grid using a methyl probe as charge +1. In order to evaluate the QSAR model externally, data set was divided into training and test set using sphere exclusion methods. Training set is used to develop the QSAR model for which biological activity data are known. Test set is used to challenge the QSAR model developed based on the training set to assess the predictive effectiveness of the model which is not included in model generation. Sphere exclusion algorithm was used for creation of training and test sets. Sphere exclusion algorithm[22] allows constructing training sets covering all descriptor space areas occupied by representative points. The higher the dissimilarity level, the smaller the training set is and the larger the test set is and vice versa.

Model Building: Data generated by k nearest neighbor molecular field analysis (kNN-MFA) in conjunction with stepwise (SW) forward-backward, simulated annealing (SA) and genetic algorithm (GA) variable selection methods with pIC50 activity field as dependent variable and descriptors as independent variable [23-25]. Different training and test set of substituted 1,3-diaryl propenone derivatives as antimalarial agent derivatives were constructed using

sphere exclusion with dissimilarity level 13. Training and test set were selected and calculated Unicolumn statistics (table 2).

Table 2: Uni-Column Statistics for Model 1 for training and test set activity

Column Name	Average	Max	Min	Std Dev	Sum
Training set	5.2645	5.8181	4.9090	0.2634	63.1738
Test set	5.1991	5.2881	5.1101	0.1259	10.3982

RESULTS AND DISCUSSION

The QSAR studies was performed at different dissimilarity value, best model selected on the basis of statistical predicted value, training and test set of substituted 1,3-diaryl propenone derivatives as antimalarial agent derivatives were constructed using sphere exclusion (dissimilarity level 13). Training and test set were selected if they follow the Unicolumn statistics, i.e., maximum of the test is less than maximum of training set and minimum of the test set is greater than of training set, which is prerequisite for further QSAR analysis shown in table 2. The most significant model is + Model 1 showed (test set=01, 02 and 03) that steric (S_584) and electrostatic (E_295) interactions play important role in determining as antimalarial activity. The most significant values of model 1 generated are internal predictivity 64.24% (q2 =0.64.24) and external predictivity 61.57 % (pred_r2 = 0.6157).This result shows that the test is interpolative i.e., derived from the min-max range of training set. The mean and standard deviation of the training and test set provides insight to the relative difference of mean and point density distribution of the two sets. k-Nearest neighbor molecular field analysis (kNN-MFA) was applied using stepwise (SW), simulated annealing (SA) and genetic algorithm (GA) approaches for building QSAR models. Results of models developed by SW-kNN MFA, SA-kNN MFA and GA-kNN MFA using sphere exclusion methods. Significant QSAR model generated.

Figure 2: Graphical fitness plot between actual and predicted activity values as antimalarial activity

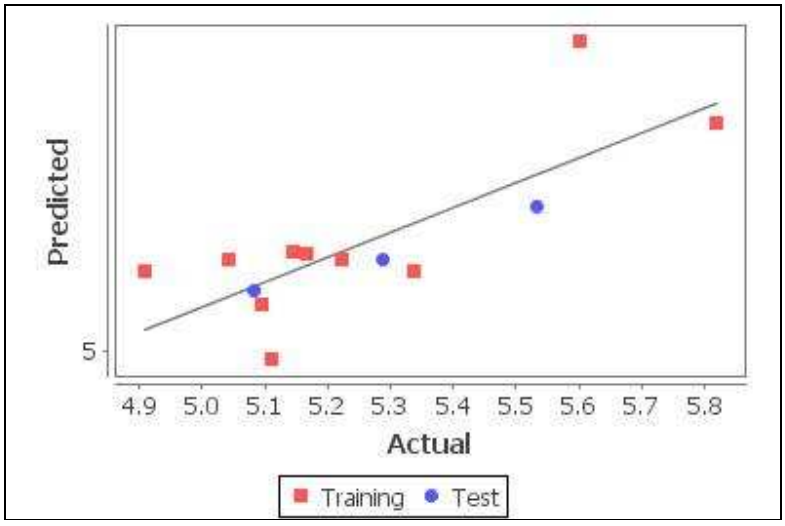


Table 3: Actual and predicted biological activity for Training set and test set

S. No.	Actual	Predicted			Residue		
		SW-KNN MFA	GA-KNN MFA	SA-KNN MFA	SW-KNN MFA	GA-KNN MFA	SA-KNN MFA
1	5.533	5.27368	5.34775	5.42891	0.25932	0.18525	0.10409
2	5.602	5.74554	5.74358	5.40479	-0.14354	-0.14158	0.19721
3	5.11	4.97742	4.97742	5.56982	0.13258	0.13258	-0.45982
4	5.221	5.21775	5.23425	5.43648	0.00325	-0.01325	-0.21548
5	5.041	5.37227	5.23425	5.4359	-0.33127	-0.19325	-0.3949
6	5.083	5.23907	5.14422	5.41278	-0.15607	-0.06122	-0.32978
7	5.818	5.54613	5.54376	5.33226	0.27187	0.27424	0.48574
8	5.288	5.29045	5.21775	5.50934	-0.00245	0.07025	-0.22134
9	4.909	5.18999	5.19033	5.22204	-0.28099	-0.28133	-0.31304
10	5.167	5.23125	5.248	5.10181	-0.06425	-0.081	0.06519
11	5.145	5.23675	5.2535	5.14725	-0.09175	-0.1085	-0.00225
12	5.222	5.2175	5.23425	4.9091	0.0045	-0.01225	0.3129
13	5.337	5.18875	5.2055	5.13455	0.14825	0.1315	0.20245
14	5.095	5.10958	5.10958	5.16958	-0.01458	-0.01458	-0.07458

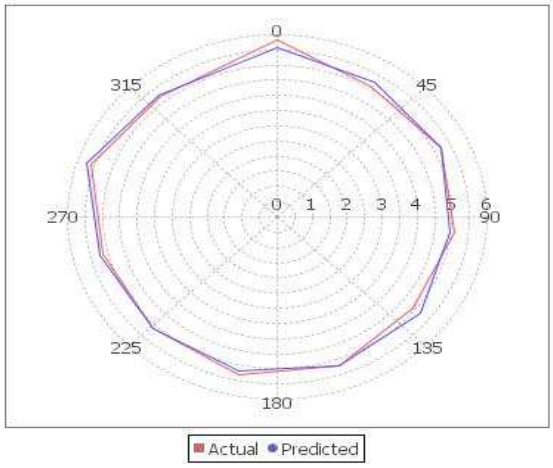
Statistical measures used to correlate biological activity and molecular descriptors. Data fitness plot for model is shown in figure 2. Result of the observed and predicted biological activity for the training and test compounds for the Model is shown in table 3. The plot of observed vs. predicted activity of training and test sets for model is shown in figure 3. From the plot it can be seen that kNN-MFA model is able to predict the activity of training set quite well (all points are close to regression line) as well as external. Sphere exclusion (SE) algorithm and random selection methods were used for constructing training and test sets. kNN-MFA methodology with stepwise (SW), simulated annealing (SA) and genetic algorithm (GA) was used for building the QSAR models and alignment molecule with descriptor shown in figure 4.

Model 1 for SW-kNN MFA
$pIC_{50} = q^2 = 0.6457$; Pred $r^2 = 0.6157$; Ftest=88.6; ZScore=98; training =11, test=3 (01, 02 and 03)

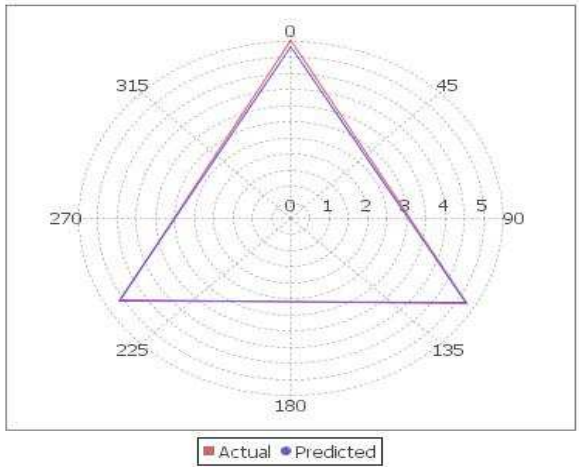
Model 2 GA-kNN MFA
$pIC_{50} = q^2 = 0.5278$; Pred $r^2 = 0.\ 0.534$; Ftest=81.6; ZScore=57; training =11, test=3 (01, 02 and 03)

Model 3 for SA-kNN MFA
$pIC_{50} = q^2 = 0.6198$; Pred $r^2 = 0.4581$; Ftest=95.6; ZScore=48; training =11, test=3 (01, 02 and 03)

Figure 3: Training set (A) and Test set (B) biological activity is predicted graph



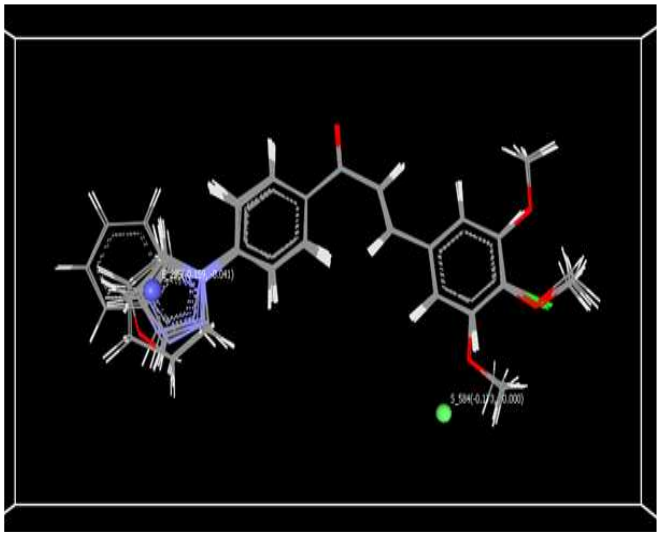
A



B

The model 1 was considered to be best model in evaluation of predicted values. The steric (S_584) presented on the phenyl ring indicates that the bulky group is necessary for enhancing the activity. If at R_1, R_2, R_3 position methyl group and long chain is than there is change in biological activity. Electrostatic (E-295) indicates that electron withdrawing groups are required for enhancing the biological activity. At R functional group Cl, F and other electron withdrawing groups enhances the activity. The kNNMFA contour plot provided further understanding of the relationship between structural features of substituted 1,3-diaryl propenone derivatives as antimalarial agent derivatives and their activities which should be applicable to design newer potential as as antimalarial agent.

Figure 4: Showing 3D-Allignment of molecules and descriptor of model by wire frame model



CONCLUSION

Model developed evaluate biologically a series of analogs of 1,3-diaryl propenone derivatives by modifying systematically the molecule, in order to explore the SAR of these derivatives. In order to determine the better structural characteristics that were able to improve the antimalarial activity and to investigate the effects of different chemical modifications, an extensive SAR was examined by varying the nature and the position of the substituents both on the basic moiety.

The master grid obtained for the various kNN-MFA models show that positive range in steric descriptors indicates bulky substituents group is preferred in R_1, R_2 and R_3. On the basis of the electrostatics near to ring at R the electron withdrawing group is required as Cl, F and COOH with heterocyclic ring. Steric and electrostatic potential contributions to the developed model in this work is useful in describing QSAR of substituted 1,3-diaryl propenone derivatives as antimalarial agent and can be employed to design new derivatives with potent inhibitory activity.

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