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Prediction of 4-(5-trifluoromethyl-1*h*-pyrazol-1-yl)-Chloroquine analogues as Antimalarial activity

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Abstract: The analysis using k nearest neighbor molecular field analysis (kNN-MFA) method was performed on a series of 4-(5-trifluoromethyl-1*h*-pyrazol-1-yl)-chloroquine 18 derivatives as antimalarial agent using molecular design suite (VLifeMDS 4.1.19092011). The significant statistical model 4 showed that steric bulky and electrostatic electron withdrawing functional group near pyrazol ring play important role in determining antimalarial activity and functional requirement. The most significant values of model generated are internal predictivity 58.55% (q^2 =0.5855) and external predictivity 86.27 % (pred_r^2 = 0.86.27). The contour plots required for further understanding of the relationship between structural requirement of derivatives and their biological activities which should be helpful to design novel antimalarial agent.
Keywords: 3D-QSAR, kNN-MFA, antimalarial, design, novel.

INTRODUCTION

Malarial is caused by several *Plasmodium* parasite species out of which *falciparum* is most common. Malarial is a dreadful disease kills millions of people every year, world-wide coming out of chloroquine-resistant variants of *Plasmodium falciparum* has inspired for development of novel and safer efficient drug against malaria[1]. The resistance to this drug has not been properly known clinically so faraway. Malaria parasites mostly depend on organic material, purines and pyrimidines for their DNA and RNA synthesis and repairing.

The malarial parasite receives purines from the host, while pyrimidines synthesis by de novo process in their own body[2-7]. In difference, mammalian cells can use synthesized pyrimidine bases and nucleosides salvage pathways[3,4,7]. The chloroquine only synthetic antimalarial drug which cured malaria for several years has now fallen into category of resistance drug[8-10]. The decrease in action of chloroquine there is transformed interest to look for alternate synthetic and reasonably priced medicines for malaria treatment.

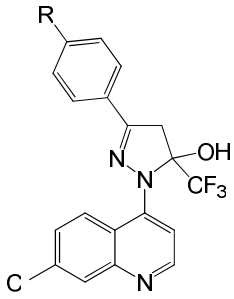
Therefore, there is a immense need to prepare new antimalarial agents due resistance in some of previous available drug[11,12]. The QSAR suggestion helps in development of novel antimalarial agent.

MATERIALS AND METHODS

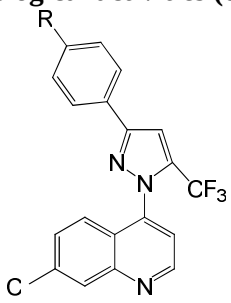
Data Set

In the current study a dataset of 18 molecules of 4-(5-trifluoromethyl-1*h*-pyrazol-1-yl)-chloroquine derivatives[13] has been taken from the previous reported literature for QSAR studies presented in table 1. The biological activity IC_{50} µM values have been converted to the pIC_{50} for generation of the QSAR model.

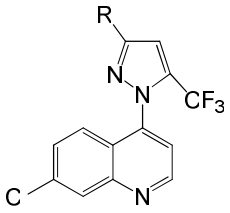
Table 1: General structure of the compounds of 4-(5-trifluoromethyl-1*h*-pyrazol-1-yl)-chloroquine derivatives and their biological activities (data set of 18 molecules)



2a-2h



3a-3h



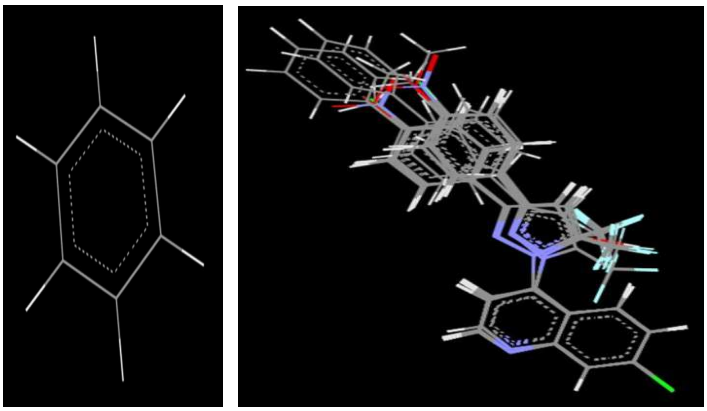
3i, 3j

S. No	Compond	Ar	IC_{50} µM	pIC_{50}
1.	2a	H	1.39	5.8523
2.	2b	Me	3.04	5.5171
3.	2c	F	2.13	5.6716
4.	2d	Cl	1.69	5.7721
5.	2e	Br	1.55	5.8096
6.	2f	OMe	50	5.3010
7.	2g	NO_2	5.71	5.2433
8.	2h	Ph	2.12	5.6736
9.	3a	H	9.53	5.0209
10.	3b	Me	50	5.3010
11.	3c	F	27.62	4.5686
12.	3d	Cl	50	5.3010
13.	3e	Br	50	5.3010
14.	3f	OMe	50	5.3010
15.	3g	NO_2	50	5.3010
16.	3h	Ph	18.53	4.7321
17.	3i	Me	4.29	5.3675
18.	3j	Napthyl	50	5.3010

QSAR Studies:

QSAR studies performed by kNN-MFA method using the software Molecular Design Suite of V-life (MDS) 4.1.19092011.[14]

In analysis it was necessary to align the structure on the common template. The chosen dataset were aligned by template based alignment method using most active molecule **18** as a reference molecule and benzene ring as a template. The alignment of all the molecules on the template (1) is shown in figure 1 as a reference aligned molecule (2). In the aligned molecules, a molecular field is computed on a grid of points in space around the molecule and calculated descriptors (steric, electrostatic and hydrophobic) interaction energies using a CH_3 probe of charge +1.



1 2

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

For proper calculation of the QSAR analysis the dataset was divided into the training and test set. In order to evaluate and validate the QSAR model internally and externally, dataset was divided into different training and test set by sphere exclusion methods respectively. The training set provides external validation while test set provides internal validation. As the dissimilarity values fluctuate or increases, the smaller the training set is and the decreases the test set are and vice versa.

Different training and test set of 4-(5-trifluoromethyl-1*h*-pyrazol-1-yl)-chloroquine derivatives were created by sphere exclusion with dissimilarity level 4.6 to 12. Training and test set were selected and calculated Unicolumn statistics.

The statistical significance model developed by k nearest neighbor molecular field analysis (kNN-MFA) in combination with stepwise (SW) forward-backward, simulated annealing (SA) and genetic algorithm (GA) variable selection methods with pIC_{50} activity field as dependent variable and steric, electrostatic and hydrophobic descriptors as independent variable[16-18].

RESULTS AND DISCUSSION

In the QSAR study a dataset of 4-(5-trifluoromethyl-1*h*-pyrazol-1-yl)-chloroquine derivatives[13] selected and reported biological activity IC_{50} µM values, have been converted to the pIC_{50} for generation of the statistical significant model. In the analysis several training and test set of 4-(5-trifluoromethyl-1*h*-pyrazol-1-yl)-chloroquine derivatives were created by sphere exclusion (dissimilarity level 4.6 to 12). Training and test set were chosen if they follow the pattern of Unicolumn statistics, i.e., minimum of the test is more than minimum of training set and maximum of the test set is lesser than of training set, which is requirement for QSAR model generation and analysis shown in 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	5.4352	6.7212	4.5686	0.4818	86.9629
Test set	5.5366	5.7721	5.3010	0.3331	11.0731

Results of models developed by SW-kNN MFA, SA-kNN MFA and GA-kNN MFA in linked with sphere exclusion methods. In all three methodologies SW-kNN MFA showed significant statistical model which was explained here, QSAR model 4 developed is shown in table 3. The statistical significant model **4** with dissimilarity level 9 and test set 3b, 2d and 2a showed that steric (S_350) and electrostatic (E_551) positive interactions play vital role in recognizing antimalarial activity. The statistical significant model **4** generated with

internal predictivity 58.55% (q^2 =0.5855) and external predictivity 86.27 % (pred_r^2 = 0.86.27). This result shows that the training is resulting from the max-min range of test set.

Table 3: Result of kNN-MFA study using sphere exclusion selection method

S. No	Dissimilarity value	Test set	SW-kNN MFA		GA-kNN MFA		SA-kNN MFA	
			q^2	$Predr^2$	q^2	$Predr^2$	q^2	$Predr^2$
1.	4.6	3b, 2d	0.2512	-1.3164	-0.2780	-0.3691	0.1873	0.7580
2.	5	3b, 2d	0.2906	-0.4132	-0.0098	-0.0031	0.3057	0.6457
3.	7	3b, 2a	0.2936	-0.3552	-0.3941	-0.0115	0.3177	0.840
4.	**9**	**3b, 2d, 2a**	**0.5855**	**0.8627**	**0.5390**	**0.689**	**0.5127**	**0.7642**
5.	9.5	2b, 2e, 2g, 2d, 3b, 3e	0.4855	-0.1149	0.5432	0.1267	0.4273	0.3217
6.	10	2b, 2c, 2d, 2e, 3b, 3c, 3e	0.2568	0.4351	0.0125	0.4389	0.4093	0.4634
7.	11	2b, 2c, 2d, 2e, 3b, 3c, 3e	0.2568	0.4351	-0.0853	0.3740	0.5655	0.4896
8.	11.5	2b, 2c, 2d, 2e, 3b, 3c, 3e, 3d	0.2568	0.4276	-0.3452	0.1358	0.3715	0.3221
9.	12	2b, 2c, 2d, 2e, 2f, 3b, 3c, 3e, 3d	0.6750	0.2699	0.3257	0.2257	0.3612	0.3747

The statistical models used in analysis are shown in table 4 to correlate biological activity and steric and electrostatic descriptors. The result of the actual and predicted (pred.) biological activity and residual value (res.) for the test and training compounds for the Model 4 is shown in table 4. The data fitness plot for model 4 with training and test set is shown in figure 2.

Table 4: Actual and predicted biological activity for Training set and test set.

S. No	Comp	Actual	SW-KNN MFA		GA-KNN MFA		SA-KNN MFA	
			Pred.	Res.	Pred.	Res.	Pred.	Res.
1	2a	5.8523	5.62781	0.22449	5.73992	0.11238	5.35739	0.49491
2	2b	5.5171	5.75337	-0.23627	5.69936	-0.18226	5.61773	-0.10063
3	2c	5.6716	5.53537	0.13623	5.6494	0.0222	5.20738	0.46422
4	2d	5.7721	5.6159	0.1562	5.67424	0.09786	5.50518	0.26692
5	2e	5.8096	5.48933	0.32027	5.69512	0.11448	5.25118	0.55842
6	2f	5.3010	5.39979	-0.09879	5.42547	-0.12447	5.08237	0.21863
7	2g	5.2433	4.96594	0.27736	5.34221	-0.09891	5.3059	-0.0626
8	2h	5.6736	5.66523	0.00837	5.73104	-0.05744	5.25363	0.41997
9	3a	5.0209	4.9754	0.0455	5.26065	-0.23975	5.47335	-0.45245
10	3b	5.3010	4.94638	0.35462	5.37205	-0.07105	5.54301	-0.24201
11	3c	4.5686	5.16097	-0.59237	4.85884	-0.29024	5.46028	-0.89168
12	3d	5.3010	5.31281	-0.01181	5.71794	-0.41694	5.31118	-0.01018
13	3e	5.3010	4.94258	0.35842	4.90217	0.39883	5.48525	-0.18425
14	3f	5.3010	5.30391	-0.00291	5.30387	-0.00287	5.32376	-0.02276
15	3g	5.3010	5.30545	-0.00445	5.31487	-0.01387	5.25825	0.04275
16	3h	4.7321	5.12347	-0.39137	4.92347	-0.19137	5.51402	-0.78192
17	3i	5.3675	5.18569	0.18181	5.28549	0.08201	5.51134	-0.14384
18	3j	5.3010	5.24076	0.06024	5.33707	-0.03607	5.4994	-0.1984

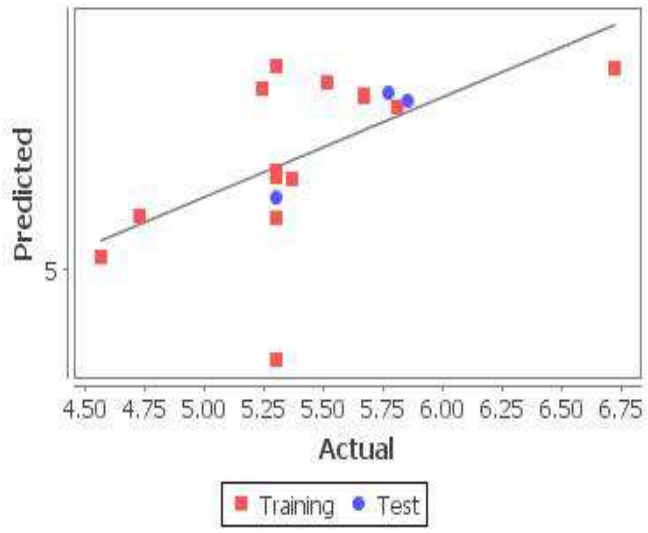


Figure 2: Graphical fitness plot between actual and predicted activity values for antimalarial

The analysis generated by kNN-MFA model 4 is able to calculate the internal significant activity of training set and test set fairly when all points are near to regression line for internal and external validation respectively (figure 3).

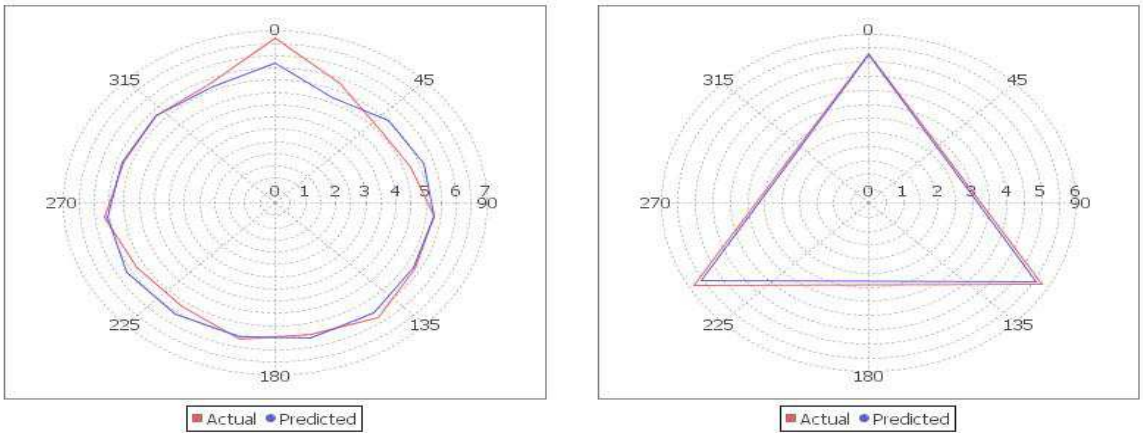


Figure 3: Training set (A) and Test set (B) biological activity is predicted graph.

Sphere exclusion (SE) algorithm was used for generation of 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 database alignment molecule with steric and electrostatic descriptor shown in figure 4. The steric descriptor (S_350; S_435) showed that bulky groups and electrostatic (E_550, 551) revealed electron withdrawing group required for enhancing the biological activity near the pyrazol ring.

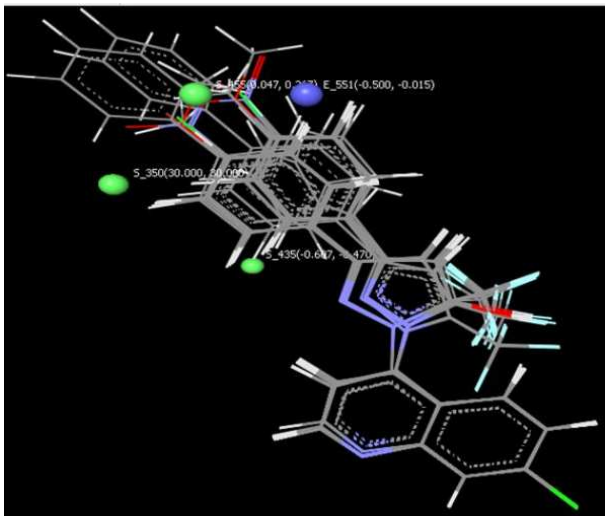


Figure 4: Showing 3D-Allignment of molecules and descriptor of model by wire frame model

The kNN-MFA statistical model and contour plot (figure 5) provided further information regarding of the relationship between structural requirement of 4-(5-trifluoromethyl-1*h*-pyrazol-1-yl)-chloroquine derivatives and their biological activities which should be applicable to design and development of novel potential as antimalarial activity.

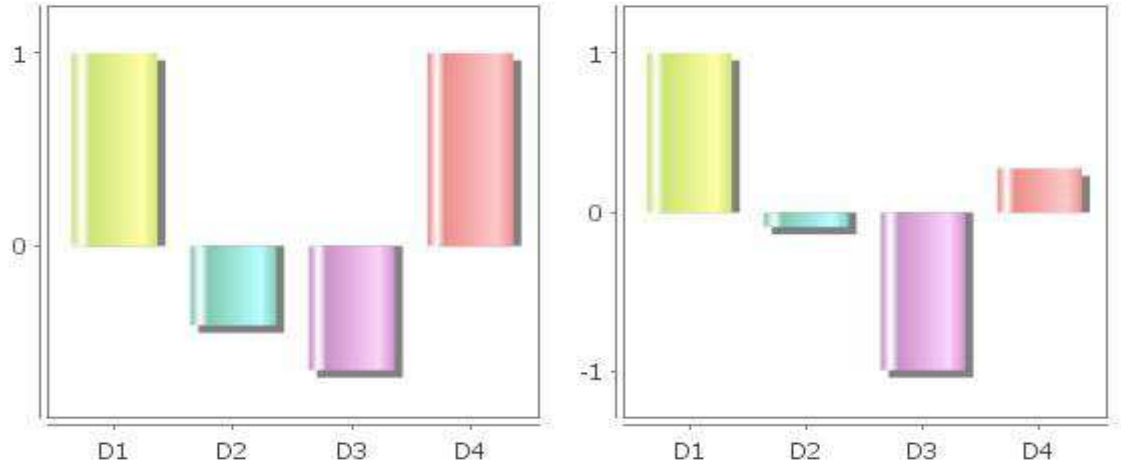


Figure 5: The kNN-MFA contour plots shows structural features of derivatives and their activities.

CONCLUSION

The statistical model developed to predict the structural requirement of 4-(5-trifluoromethyl-1*h*-pyrazol-1-yl)-chloroquine derivatives to inhibit plasmodium. The kNN-MFA model 4 showed that positive response in steric descriptors indicates bulky substituents group is preferred and electrostatic descriptors revealed electron withdrawing group requirement near pyrazole ring region. The electrostatic and steric descriptor field contributions and contour map with generated model useful in describing QSAR of 4-(5-trifluoromethyl-1*h*-pyrazol-1-yl)-chloroquine derivatives as antimalarial activity and can be employed to design novel derivatives with potent inhibitory activity.

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