2D QSAR STUDY OF QUINAZOLINE DERIVATIVES AS POTENT ANTIMALARIAL AGENTS

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Abstract

Malaria is caused by a parasite called Plasmodium that is transmitted from one human to another by the bite of infected Anopheles mosquitoes. *Plasmodium falciparum*, the protozoan agent responsible for cerebral malaria, developed resistance to chloroquine. Quinazoline derivatives identified recently as potential antimalarial agents. New quinazoline derivatives displaying significant antiplasmodial properties, considering the possible affinity of such molecular scaffold for Plasmodium kinases which are parasitic targets of prime strategic importance for the future development of new antimalarial drug-compounds. Quantitative structure activity relationship (QSAR) analysis was performed on a series of 4-anilinoquinazoline for their antimalarial activity by using VLife MDS software. Generated QSAR models were based on Partial Least Squares Regression coupled with Stepwise forward-backward method. QSAR study revealed that path cluster and element count are mainly responsible for antimalarial activity. The best model showed r^2 value = 0.9917, q^2 value = 0.9415 and predicted r^2 value = 0.9042. The results obtained from QSAR studies could be used in designing better antimalarial agents in future.

Keywodrs: Quinazoline, Antimalarial, Plasmodium falciparum, Partial Least Squares Regression, QSAR.

Introduction:

Malaria causes 1 million deaths each year worldwide among about 250 million people suffering from this major parasitic infection, according to the W.H.O. [1]. Due to the ongoing development of *resistance of Plasmodium falciparum* to conventional antimalarial drugs, malaria has become a major global problem and efforts to discover new agents against multi-drug resistant Plasmodium strains are long-term and essential tasks for researchers [2]. *Plasmodium falciparum*, the protozoan agent responsible for cerebral malaria, is the most worrying species, in particular with chloroquine and multi-resistant strains such as W2. Effectively, its chemosensitivity appears nowadays as nearly limited to the single artemisin-based combination therapies. In such a context, medicinal chemists must investigate new pharmacophores in order to put forward new drug candidates presenting low costs of production which could significantly contribute to improve the sanitary situation of many developing countries.

Among the different heterocyclic structures which have been studied for their antiplasmodial properties, quinazoline has quite recently showed increasing interest [3,4]. During the last two years, our research team has particularly explored the antiplasmodial potential of the quinazoline ring [5,6], with promising results. We chose to search for new 4-anilinoquinazoline derivatives displaying significant antiplasmodial properties, considering the possible affinity of such molecular scaffold for Plasmodium kinases which are parasitic targets of prime strategic importance for the future development of new antimalarial drug-compounds [7-9].

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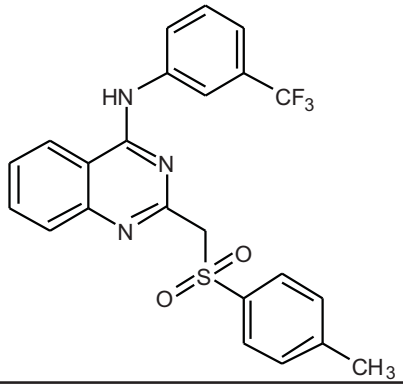
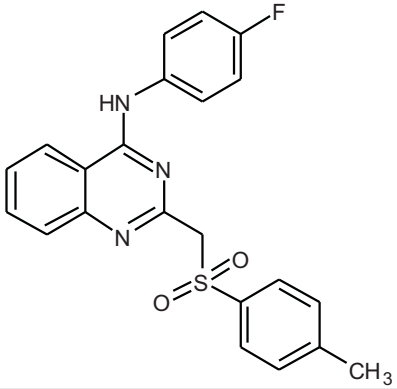
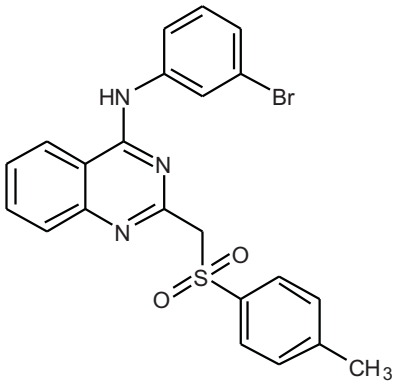
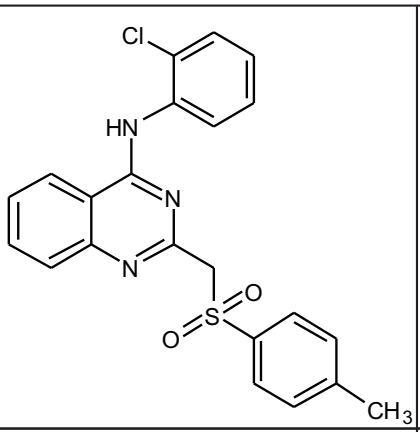
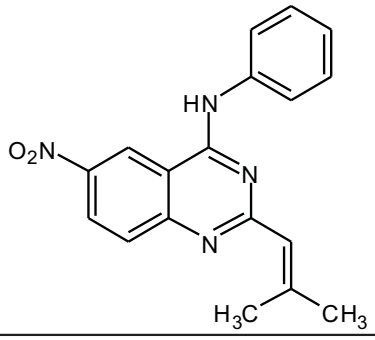
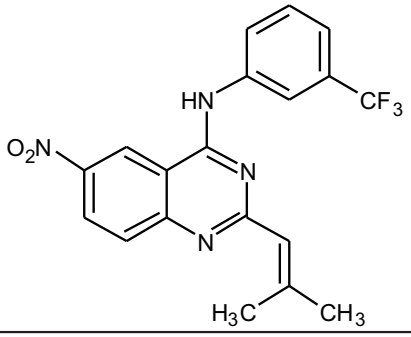
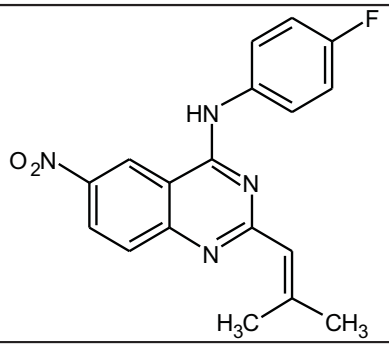
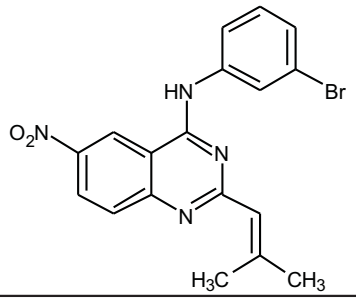
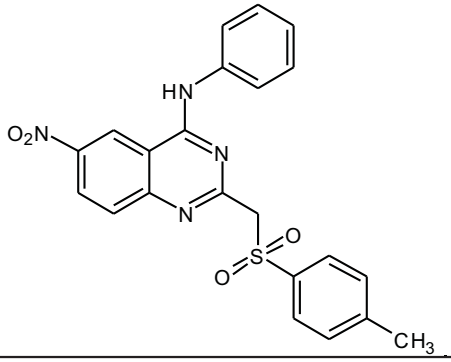
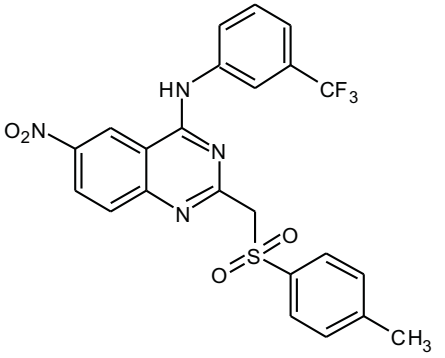
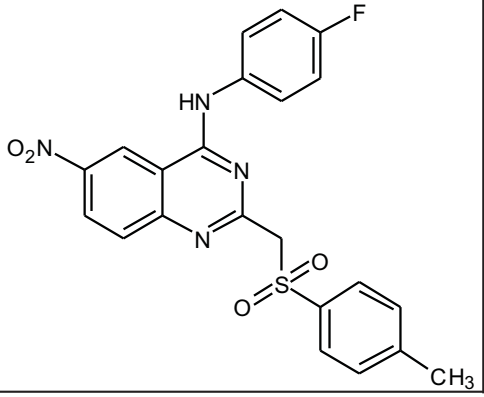
Material And Method

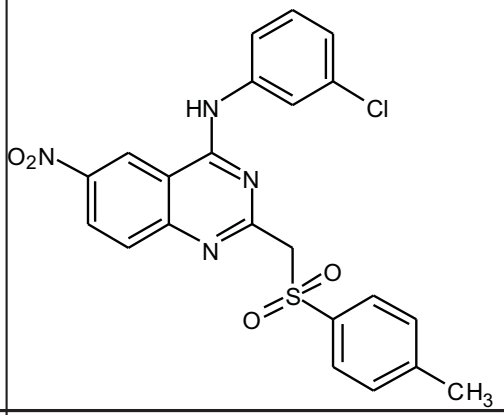
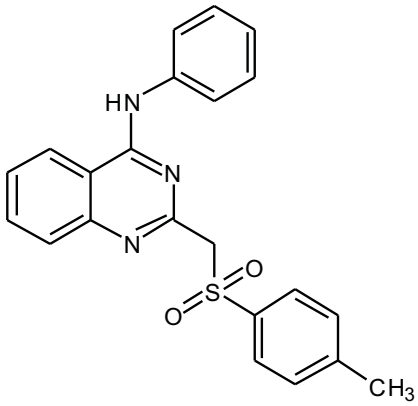
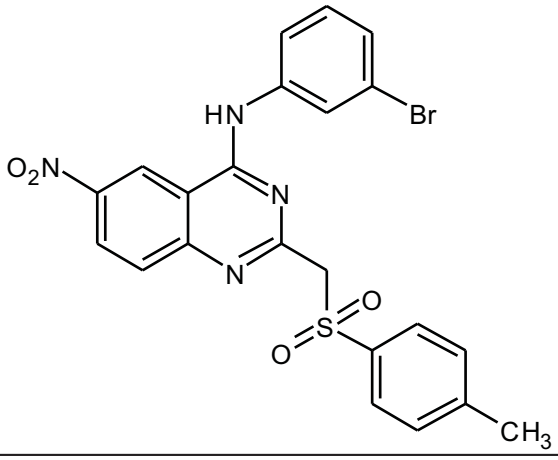
A data set of 14 molecules has been taken from published article [10]. From which only 12 compounds were used for QSAR study. Two compounds were not included in series due to undetermined activity. Antimalarial activity was expressed as IC_{50} values and was converted to negative logarithm of IC_{50}. The structures and antimalarial activity data of compounds are listed in Table 1.

Table 1: The Chemical structure and Biological activity data of compound:

Compound code	Structure	IC_{50} (μM)	-Log IC_{50} (μM)
AS01		15	-1.176
AS02		20	-1.3010
AS03		13	-1.1139

AS04		14	-1.1461
AS05		17	-1.2304
AS06		3.2	-0.5051
AS07		5.6	-0.7481

AS08		7.5	-0.8750
AS09		5	-0.6989
AS10		0.95	0.0222
AS11		2.2	-0.3424

AS12		1.3	-0.1139
AS13		-	-
AS14		-	-

Molecular Structure Generation:

All the molecular modeling and statistical analysis were performed using Vlife MDS software. The structures of the compounds were built using molecular sketching facilities provided in the modeling environment of Vlife. Energy minimization and batch optimization was carried out using Merck Molecular force field. All the molecules were initially optimized and then used for the calculation of descriptors and further QSAR study.

Parameters Used For Energy Minimization:

PARAMETER	VALUE
Force Field	MMFF (Merck Molecular Force Field)
Max. No. of cycles	1,00,000
Convergence Criteria	0.01 cal / mol A^0
Dielectric Constant	1(medium's Dielectric Constant which is 1 for vacuum)
Gradient type	Analytical

QSAR study:

All the 2D descriptors (thermodynamic, spatial, electronic and topological parameters) were calculated for QSAR analysis using Vlife MDS software. Thermodynamic parameters describe free energy change during drug receptor complex formation. Spatial parameters are the quantified steric features of drug molecules required for its complimentary fit with receptor. Electronic parameters describe weak non-covalent bonding between drug molecules and receptor.

Partial least square regression method is used to generate QSAR equation. For variable selection, stepwise forward-backward method was used.

Criteria for Selection of Model:

n = number of molecules (> 20 molecules)

K = number of descriptors in a model (statistically n/5 descriptors in a model)

df = degree of freedom (n-k-1) (higher is better)

r^2 = coefficient of determination (> 0.7)

q^2 = cross-validated r^2 (>0.5)

pred_r^2 = r^2 for external test set (>0.5)

SEE = standard error of estimate (smaller is better)

F-test = F-test for statistical significance of the model (higher is better, for same set of descriptors and compounds).

Selected Models:

In search of newer and potent antimalarial agents, QSAR investigation of quinazoline derivatives was performed by using VLife MDS 3.5 software. Several QSAR models were generated by using partial

least square regression method coupled with stepwise forward-backward method. Among the various models, two significant QSAR models were finally selected. Model summary of two best models are given below.

RESULT AND DISCUSSION:

For QSAR analysis regression was performed using IC_{50} values as dependent variables and calculated parameters as independent variables. In any thorough investigation of the effects of molecular properties, it is essential to prove that the results are both statistically valid and make chemical sense. It would be appropriate to obtain insight into the physical meaning of the correlation obtained as an output of the regression analysis. The magnitude of a descriptor could be used as a guideline to improve the antimalarial activity of molecules.

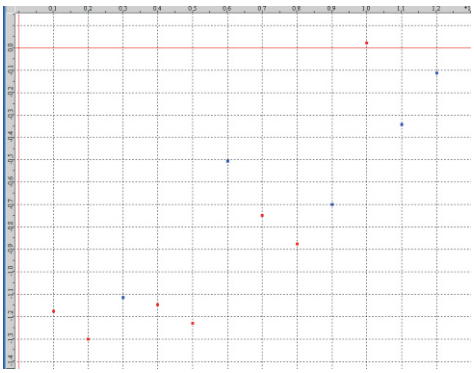
Among the generated QSAR models; two models were selected on the basis of various statistical parameters such as squared correlation co-efficient (r^2) which is relative measure of quality of fit. Fischer's value (F test) which represents F-ratio between the variance of calculated and observed activity, standard error (r^2_se) representing absolute measure of quality of fit, and cross-validated square correlation co-efficient (q^2), standard error of cross-validated square correlation co-efficient (q^2_se), predicted squared regression (pred_r^2) and standard error of predicted squared regression (pred_r^2se) to estimate the predictive potential of the models respectively.

The best two QSAR equations are discussed below:

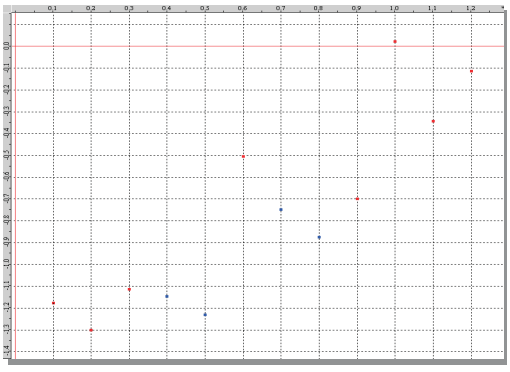
Unicolumn statistics:

Model No	Set	Column Name	Average	Max	Min	Std Dev	Sum
ASR29	Training	pIC_{50}	-0.8063	0.0222	-1.3010	0.4336	-6.4502
	Test	pIC_{50}	-0.6946	-0.1139	-1.1760	0.5468	-2.7784
A4S	Training	pIC_{50}	-0.6536	0.0222	-1.3010	0.5033	-5.2290
	Test	pIC_{50}	-0.9999	-0.7481	-1.2304	0.2262	-3.9996

Activity distribution graph:



Model ASR29



Model A4S

Statistics:

Model No.	r^2	q^2	Pred r^2	O.C.	N	DOF	F-Test
ASR29	0.9917	0.9415	0.9042	1	7	5	600.5639
	(0.0459)	(0.1222)	(0.1736)				
A4S	0.8996	0.8350	0.8632	1	8	6	53.7679
	(0.1722)	(0.2208)	(0.1699)				

Where n = number of molecules, r^2 = coefficient of determination, q^2 = cross-validated r^2, pred_r^2 = r^2 for external test set, O.C. = optimum components, DOF= degree of freedom, F-test = F-test for statistical significance of the model (higher is better). Values in bracket are standard error of estimate (r^2se, q^2se, pred_r^2se respectively).

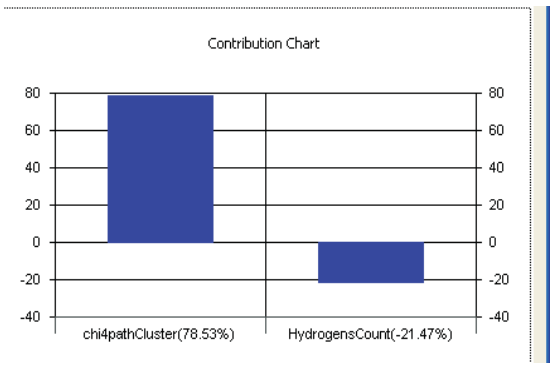
Equations:

Model No.	Equation
ASR29	pIC_{50} = +1.0413 chi4pathcluster-0.0889 HydrogensCount -3.2334.
A4S	pIC_{50} = +1.0036 chi4pathcluster-4.6731.

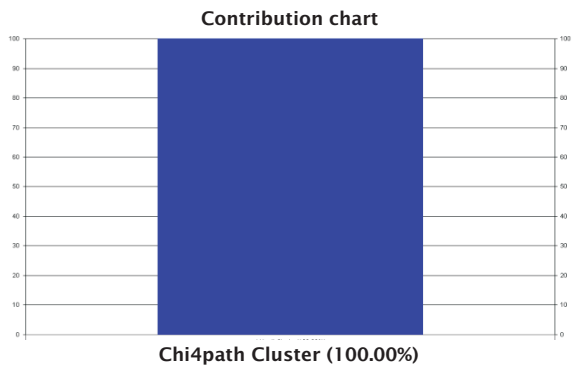
Correlation matrix:

	chi4pathCluster	HydrogensCount	Score
chi4pathCluster	1	0.017298	2
HydrogensCount	0.017298	1	2

Contribution chart:



Model ASR29



Model A4S

Contribution chart values:

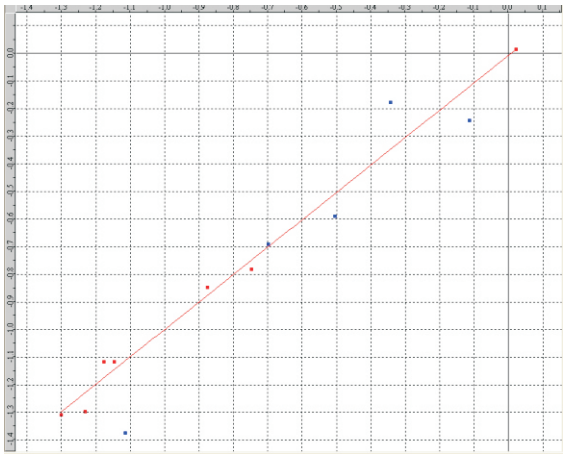
Model No.	Descriptors	
	Chi4pathcluster	HydrogensCount
ASR29	78.53%	-21.47%
A4S	100%	-

Actual-predicted activity table:

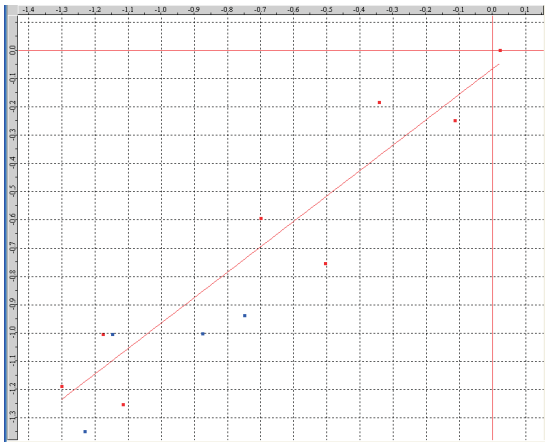
Compound code	Actual activity In IC_{50} (nM)	Model ASR29		Model A4S	
		Predicted activity	Residual	Predicted activity	Residual
AS01	-1.176	-1.11718	-0.05882	-1.00484	-0.17116
AS02	-1.301	-1.30844	-0.00744	-1.18917	-0.11183
AS03	-1.1139	**-1.37503**	0.26113	-1.25335	0.13945
AS04	-1.1461	-1.11703	-0.02907	**-1.00469**	-0.14141
AS05	-1.2304	-1.29583	0.06543	**-1.34845**	0.11805
AS06	-0.5051	**-0.59052**	0.08542	-0.7544	0.2493
AS07	-0.7481	-0.78178	0.03368	**-0.93873**	0.19063
AS08	-0.875	-0.84836	-0.02664	-1.00291	0.12791
AS09	-0.6989	**-0.69104**	-0.00786	-0.59413	-0.10477
AS10	0.0222	0.014271	0.007929	-0.000075	0.022125
AS11	-0.3424	**-0.17699**	-0.16541	-0.18441	-0.15799
AS12	-0.1139	**-0.24358**	0.12968	-0.24858	0.13468

Predicted activity in the bold indicates test set.

Fitness plot:



Model ASR29



Model A4S

Descriptor contribution:

1. chi4pathCluster: This descriptor signifies molecular connectivity index of 4th order pathcluster.
2. HydrogensCount: This descriptor signifies number of hydrogen atoms in a compound.

Two descriptors (chi4pathcluster and hydrogens count) are present in the models ASR29 and only one descriptor (chi4pathcluster) is present in model A4S.

From the four series fragments that have been given by Hall and Kier[11], chi4pathcluster was found to be predominating for the good antimalarial activity. As in equation chi4pathcluster was found to be positive, hence increasing the value of this descriptor will provide the potent compound as antimalarial agent. Apart from this chi4pathcluster was found to be significant in both models with high contribution value. Similarly in equation Hydrogens Count was found to be negative, hence decreasing the value of this descriptor will provide potent compound.

The statistical measures determine the estimation power of model for the same data from which it has been determined and evaluate it only internally. On the other hand, cross-validated parameters determine the prediction power for the data not included in deriving the model and evaluate the model externally to avoid chance of correlation completely. It can be observed that the overall statistics of the equation generated in PLS regression analysis are excellent and their prediction ability is also significant.

Conclusion:

In summary, from the derived QSAR model it can be concluded that antimalarial activity by the quinazoline derivatives is strongly influenced by physicochemical descriptors. The generated QSAR model on the data set with reasonable chemical diversity and biological activity demonstrated a promising method and the descriptors chi4pathcluster and hydrogens count were found to be important in describing antimalarial activity. Pattern of substitution can be extracted from the developed model. The descriptors showed by QSAR study can be used further for study and designing of new compounds. Consequently this study may prove to be helpful in development and optimization of existing antimalarial activity of this class of compounds.

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Abbreviations:

QSAR	:	quantitative structure activity relationship
PLS	:	partial least square regression
DOF	:	degree of freedom
r^2	:	square of correlation coefficient
q^2	:	cross validated r^2
Pred r^2	:	square correlation coefficient of test set
F-Test	:	Fisher test
O. C.	:	Optimum component

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