Asian Pub. Corp.

www.asianpubs.org

ARTICLE

QSAR Analysis of 7-Chloro-4-Aminoquinoline Derivatives as Antimalarial Agents

Mithun Rudrapal✉ and Dipak Chetia

Asian Journal of Organic & Medicinal Chemistry

Volume: 1 Year: 2016
Issue: 2 Month: April-June
pp: 51-54
DOI: http://dx.doi.org/10.14233/ajomc.2016.AJOMC-P16

Received: 15 May 2016
Accepted: 15 June 2016
Published: 2 July 2016

ABSTRACT

Quantitative structure activity relationship (QSAR) studies were performed on a series of 7-chloro-4-aminoquinoline derivatives with aim to evaluate the influence of steric (MR), hydrophobic (log P) and electronic (DM) factors on their antimalarial activity. A multiple linear regression analysis (MLR) was carried out to obtain QSAR model(s) in order to make quantitative assessment of relationships between above molecular descriptors and antimalarial activity of 4-amino-quinoline derivatives. QSAR models were found statistically significant which, therefore, may be useful for the prediction of activity of some newer structural analogues based upon the structural scaffold of 7-chloro-4-aminoquinoline for the rational design and development of potent antimalarial leads.

KEYWORDS

QSAR, Multiple linear regression analysis, Molecular descriptors, 7-Chloro-4-aminoquinoline, Antimalarial.

INTRODUCTION

Despite the availability of a number of antimalarial drugs, malaria still remains a major infectious disease burden around the world. Malaria infects 300-600 million people and kills about three million people in a year globally [1]. The spread of resistance of malaria parasites is attributed to be the main complicating factor in malaria chemotherapy using existing drugs. Chloroquine, a synthetic 4-aminoquinoline antimalarial, had been the mainstay in malaria treatment because of its excellent clinical efficacy and cost-effectiveness. Because of the increasing emergence of multiple-drug resistant strains, especially *Plasmodium falciparum* the efficacy of chloroquine and related 4-aminoquinoline antimalarials has been significantly reduced in most of the malaria endemic areas of the world. Several new series of 4-aminoquinoline derivatives with bulky substituents (heteroaryl system) in the aminopropyl side chain moiety have therefore been investigated, developed and reported to be active against both sensitive- and resistant-strains of *P. falciparum*. Literature suggest that the presence of 7-chloro-4-aminoquinoline nucleus together with bulky (heteroaryl) side chain moiety is considered to be obligatory for their antimalarial activity, particularly by inhibiting the heme polymerization target of the parasite [2-4].

Author affiliations:

Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh-786 004, India

✉To whom correspondence to be addressed:

E-mail: rudrapal.m03@gmail.com

Available online at: http://ajomc.asianpubs.org

Quantitative structure-activity relationship (QSAR) is a valuable tool in rational drug design (RDD), which relies on the basic assumption that molecules with similar structures or physico-chemical properties will have similar type of pharmacological activities. The basic principle of QSAR technique involves building mathematical relationship between biological activity data of a series of compounds and their structures defined by molecular/structural descriptors [5]. Once a reliable QSAR model is established, it can be useful to predict the activities of molecules and know which structural features play an important role (degree of activity) in biological processes.

In our earlier studies, we synthesized some new 4-aminoquinoline derivatives with modification at the C-2 substituted six-membered 1,3-thiazinan-4-one ring system at the aminopropyl side chain. They were evaluated for *in vitro* antimalarial activity against *P. falciparum* 3D7 strain. In continuation of that, present investigation was aimed to establish the QSAR models in order to predict their antimalarial activity against *P. falciparum*. The steps involved in QSAR analysis are data collection, selection and procurement of molecular descriptor, correlation model development and finally model evaluation. Multiple linear regression (MLR) models were developed as mathematical equations and an attempt was made to relate the chemical structure (structural descriptors) of the compounds with their physico-chemical and biological (% inhibitory activity) properties.

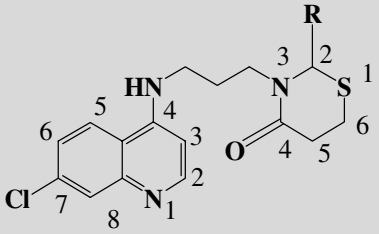
EXPERIMENTAL

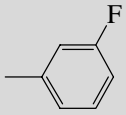
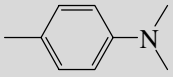
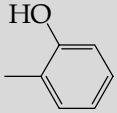
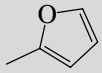
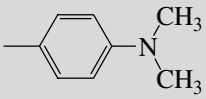
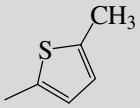
QSAR studies on a new series of 4-aminoquinoline derivatives was carried out for their antimalarial activity as dependant variable and different physico-chemical (structural) parameters (MR, log P, DM) as independent variables in COMPAQ Presario CQ 42 PC using MS Excel 2007, ChemDraw Ultra 8.0 and SPSS software (version 18.0).

Data set: A data set of seven molecules (**1a-g**) was taken from published results [3]. The structure of the reported compounds along with their antimalarial activity data are reported in Table-1. For QSAR studies, logarithmic value of biological activity (log BA) was taken, while BA is expressed as percent inhibition of parasite growth at 50 mg/mL concentration of synthesized compound.

Molecular modeling: The structures of the compounds were constructed using ChemDraw Ultra 8.0 and transferred to Chem3D Ultra 8.0 to convert them into 3D structures. The energy minimization of the molecules was done using MM2 force field followed by semi empirical AM1 (Austin model) Hamiltonian method available in MOPAC module by fixing root mean square gradient (RMS) as 0.1 and 0.0001 kcal/mol respectively. Thus, most stable structure (having lowest energy) for each compound was generated and used for calculating various molecular descriptors like steric (molar refractivity, MR), hydrophobic (logarithmic value of partition coefficient,

TABLE-1
QSAR PARAMETERS AND ANTIMALARIAL ACTIVAITY OF
3-(3-(7-CHLOROQUINOLIN-4-YLAMINO)PROPYL)-2-(SUBSTITUTED)-1,3-THIAZINAN-4-ONES



Compd.	R	BA	log BA	MR	log P	DM
1a		39.0	1.591	117.058	4.314	6.768
1b		32.0	1.505	123.305	4.029	6.687
1c		39.5	1.596	118.536	3.766	6.255
1d		38.5	1.585	109.264	2.771	6.999
1e		18.5	1.267	101.612	3.073	5.940
1f		25.0	1.397	131.271	4.440	8.217
1g		22.0	1.342	120.825	4.474	5.916

log P) and electronic (dipole moment, DM) properties. Molecular descriptors are numerical representations of molecular structures derived from steric, electronic, constitutional, topological and geometric properties of the molecules [6]. The physico-chemical and structural parameters are presented in Table-1.

Statistical methods: SPSS software (version 19.0) was used to generate QSAR models using multiple linear regression (MLR) analysis. Mono- and multi-parametric regression analysis was carried out to derive statistically significant QSAR models. From data set (Table-1, n = 7), the software produced mono-parametric (eqns. 1-3) and multi-parametric (eqn. 4-6) QSAR equations (Table-2). The significance of these QSAR equations was evaluated with regard to the following statistical parameters: correlation coefficient (r), standard error of estimation (s), squared correlation coefficient (r^2), Fisher's value (F). The ± data within parentheses represents standard error of coefficient. For testing the validity of the predictive power of MLR models cross-validation was performed using leave one out (LOO) method. The results of cross validation are the sum of squared prediction errors, called the predicted residual sum of squares (PRESS). To calculate PRESS, each observation (one BA) was individually eliminated from the training set and remaining (n-1) observations were used to calculate a regression model. This model is used to predict the BA value of the compound, which was not included in the model. The cross-validation cycle is repeated until each compound has been excluded and predicted exactly one. The difference between the actual Y value, y_{obs} and the predicted Y, y_{calc}, is called the prediction error. The sum of the squared prediction errors is the PRESS value. The smaller PRESS is, the better the predictability of the model. For evaluation of the overall analysis, the PRESS is commonly expressed as a cross-validation correlation coefficient, r^2cv. It is possible to have a high r^2 and a very low r^2cv. When this occurs, it implies that the fitted model is data dependent. This r^2cv ranges from below zero to above one.

RESULTS AND DISCUSSION

QSAR models were found statistically significant in terms of their r and F values. For monoparametric models (eqns. 1-3, Table-2), the correlation coefficient (r = 0.688 for eqn.2) and standard deviation (s = 0.143 for eqn. 3) values were found significant. An MLR equation with high r and low s value is said to be statistically significant. The study of monoparametric analysis indicates that hydrophobic parameter log P (eqn. 2) contributes antimalarial activity more significantly than steric (MR) and electronic parameters (DM). F values were found statistically less significant for these monoparammetric equations (eqn. 1-3). PRESS (residual activity) was found lowest and r^2cv was higher for eqn. 2 indicating the predictive power of the equation. However, monoparametric QSAR analysis tells us that antimalarial activity (for training set molecules) increases with respect to above three physicochemical properties of molecules in the following order: MR < DM < log P.

Similarly, in QSAR eqns. 4-6, eqn. 4 is statistically the most significant one owing to have highest r, r^2, F value and lowest s value. PRESS and r^2cv were also significant for eqn. 4. It indicates that steric parameter MR in conjunction with hydrophobic factor log P plays an important role in imparting good antimalarial activity. Eqn. 5 (MR & DM) and eqn. 6 (log P & DM) were found statistically less significant, where lower r, r^2 & F values and higher s values were obtained as compared to eqn. 4. PRESS was higher and r^2cv was lower as compared to eqn. 4. Table-3 depicts observed and calculated activity data (obtained from eqn.1-6) of training set molecules. The residual activities were for best two models, eqn. 2 (monoparametric) and eqn. 4 (multiparametric) were calculated and are given in Table-4. High agreement between experimental (observed) and predicted (calculated) inhibitory values (logarithmic) is seen (the residual values are small), which indicates the good predictability of the established models, particularly eqns. 2 and 4. For a good QSAR analysis, multiparametric study is generally

TABLE-2
STATISTICALLY SIGNIFICANT QSAR MODELS

Model No.	Regression equation	n	r	r^2	s	F	PRESS	r^2cv
1	log BA= 0.0020 (±0.006) MR + 1.231 (±0.725)	7	0.146	0.021	0.145	0.108	0.214	0.24
2	log BA= -0.0136 (±0.088) log P + 1.521 (±0.343)	7	0.688	0.0047	0.146	0.023	0.123	0.32
3	log BA= 0.0343 (±0.073) DM + 1.240 (±0.497)	7	0.203	0.041	0.143	0.215	0.256	0.12
4	log BA= 0.0086 (±0.011) MR – 0.1146 (± 0.161) log P + 0.089 (±0.902)	7	0.361	0.130	0.153	0.299	0.145	0.43
5	log BA= 0.0005 (±0.008) MR – 0.0305 (± 0.102) DM + 1.203 (±0.808)	7	0.205	0.042	0.160	0.088	0.362	0.36
6	log BA= -0.0240 (±0.098) log P – 0.0390 (± 0.084) DM + 1.301 (±0.605)	7	0.235	0.055	0.159	0.117	0.232	0.23

TABLE-3
OBSERVED AND CALCULATED ACTIVITY

Comp. code	Observed	Calculated from					
		Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
1a	1.591	1.465	1.462	1.472	0.610	1.055	0.935
1b	1.505	1.477	1.466	1.469	0.687	1.060	0.943
1c	1.596	1.468	1.469	1.454	0.993	1.071	0.966
1d	1.585	1.449	1.483	1.480	0.711	1.044	0.961
1e	1.267	1.434	1.479	1.443	0.610	1.072	0.975
1f	1.397	1.493	1.460	1.481	0.709	1.018	0.873
1g	1.342	1.472	1.460	1.442	0.615	1.082	0.962

TABLE-4
RESIDUAL ACTIVITY

Compd.	Observed	Residual activity	
		Model 2	Model 4
1a	1.591	0.129	0.981
1b	1.505	0.039	0.818
1c	1.596	0.127	0.603
1d	1.585	0.102	0.874
1e	1.267	-0.212	0.657
1f	1.397	-0.063	0.688
1g	1.342	-0.118	0.727

carried out using two or more descriptors depending on the number of observations in the data set in order to obtain a better predictive model avoiding chances of spurious correlations [6]. Moreover, a mutual correlation among MR and log P is also less as depicted in Table-5. Considering all above observations, eqn. 4 can be used a lead for predicting the activity of newer 4-aminoquinoline-based analogues of different series which may have potent antimalarial activity.

TABLE-5
CORRELATION MATRIX

	log BA	MR	log P	DM
log BA	1.000	0.145	-0.068	0.203
MR	0.145	1.000	0.821	0.595
log P	-0.068	0.821	1.000	0.228
DM	0.203	0.595	0.228	1.000

Conclusion

QSAR analysis is used to study the quantitative effects of the molecular structure of medicinal compounds on their inhibitory activity. Accurate mathematical models were developed for predicting the antimalarial activity of a new series of 7-chloro-4-aminoquinoline derivatives. QSAR models were validated by the determination of suitable statistical parameters. From the established QSAR models, it was calculated that experimental and predicted values of inhibitory activity are in close agreement with each other. QSAR models were found statistically significant which, further support their usefulness for the prediction of activity of some newer structural analogues based upon the structural scaffold of 7-chloro-4-amino-quinoline for the rational design and development of potent antimalarial leads.

REFERENCES

1. W.H.O. World Malaria Report, WHO: Geneva, Switzerland (2014).
2. S. Roy, D. Chetia, M. Rudrapal and A. Prakash, *Med. Chem.*, **9**, 379 (2013); http://dx.doi.org/10.2174/1573406411309030008.
3. M. Rudrapal, D. Chetia and A. Prakash, *Med. Chem. Res.*, **22**, 3703 (2013); http://dx.doi.org/10.1007/s00044-012-0371-9.
4. D. Sharma, D. Chetia and M. Rudrapal, *Asian J. Chem.*, **28**, 782 (2016); http://dx.doi.org/10.14233/ajchem.2016.19478.
5. C.D. Selassie, in ed.: D.J. Abraham, Drug Discovery, In: Burger's Medicinal Chemistry and Drug Discovery, Wiley Interscience, New York, edn 6, pp. 2-3 (2003) .
6. S.O. Podunavac-Kuzmanovic, D.D. Cvetkovic and D.J. Barna, *Int. J. Mol. Sci.*, **10**, 1670 (2009); http://dx.doi.org/10.3390/ijms10041670.