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ORIGINAL ARTICLE

QSAR studies of some side chain modified 7-chloro-4-aminoquinolines as antimalarial agents

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Abstract The quantitative structure–activity relationship (QSAR) analyses were carried out for a series of new side chain modified 4-amino-7-chloroquinolines to find out the structural requirements of their antimalarial activities against both chloroquine sensitive (HB3) and resistant (Dd2) *Plasmodium falciparum* strain. The statistically significant best 2D QSAR models for Dd2, having correlation coefficient (r^2) = 0.9188 and cross validated squared correlation coefficient (q^2) = 0.8349 with external predictive ability (pred_r^2) = 0.7258 and for HB3, having r^2 = 0.9024, q^2 = 0.8089 and pred_r^2 = 0.7463 were developed by multiple linear regression coupled with genetic algorithm (GA–MLR) and stepwise (SW–MLR) forward algorithm, respectively. The results of the present study may be useful on the designing of more potent analogues as antimalarial agents.

1. Introduction

Malaria is one of the most widespread diseases in the world. According to WHO estimates 40% of the world's population presently live under malarial threat (WHO, 2000). Around 300 and 500 million cases of malaria occur annually, leading to 1–3 million deaths. Its control is globally a high priority task. Although effective antimalarial agents have been known for a long time, the alarming spread of drug resistant strains of *Plasmodium falciparum*, which is the most lethal parasite species, undergoes the urgency and continuous need for the discovery of new therapeutics. A major initiative in this direction is to find enzyme targets that are critical to the disease process or essential for the survival of the parasite. Identification and design of novel chemical entities specifically affecting these targets could lead to better drugs for the treatment of malaria (Sahu et al., 2008). Among old and new drug targets of malaria, host heme molecule remains one of the most attractive target and 7-chloroquinoline compounds are very selective towards heme bindings (Vippagunta et al., 1999). So, rather than identifying new molecules for efficacy, modified 7-chloroquinolines having many advantages and efficiency are now in priority for antimalarial chemotherapy.

The quantitative structure–activity relationship (QSAR) approach helps to correlate the specific biological activities or physical properties of a series of compounds with the measured or computed molecular properties of the compounds, in terms of descriptors (Hansch et al., 2001). QSAR methodolo-

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gies save resources and expedite the process of the development of new molecules and drugs. There have been many QSAR researches related to design of anti-malarial drugs so far (Bhattacharjee et al., 2004; Dascombe et al., 2005; Katritzky et al., 2006; Adane and Bharatam, 2008; Deshpande et al., 2009) but a systematic QSAR study is yet to be carried out for series of new 4-amino-7-chloroquinolines carrying a branched or a linear side chain with two or three amino functions.

The aim of present work is to derive some statistically significant QSAR models for side chain modified 4-amino-7-chloroquinolines for their antimalarial activities and to relate antimalarial activity to its physicochemical properties. The results obtained may contribute to further designing novel antimalarial agents.

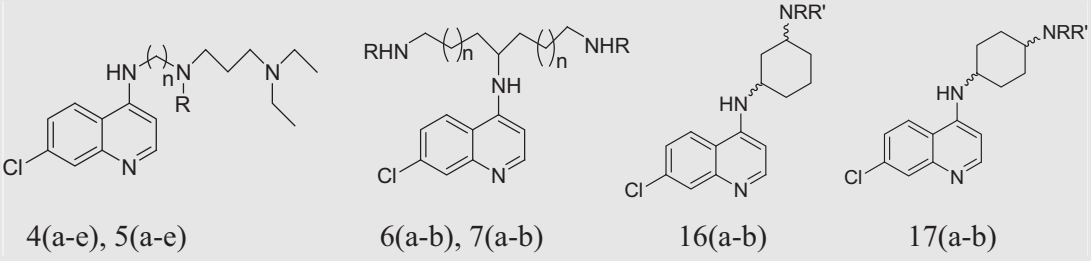
2. Experimental

2.1. Data set

A data set of 18 compounds of side chain modified 4-amino-7-chloroquinolines for antimalarial activities against chloroquine sensitive (HB3) and resistant (Dd2) *P. falciparum* strains was used for the present 2D QSAR study (Yearick et al., 2008). There is high structural diversity and a sufficient range of the biological activity in the selected series of these derivatives (Table 1). It insists as to select these series of compounds for our QSAR studies. The biological activity values [IC_{50} (nM)] reported in literature were converted to their molar units and then further to negative logarithmic scale (pIC_{50}) and subsequently used as the dependent variable for the QSAR analysis.

All 18 compounds were built on workspace of molecular modeling software VLife MDS 3.5 (Vlife Sciences Technologies Pvt. Ltd. Pune, India) and then the structure was converted to three-dimensional space for further analysis. All molecules were batch optimized for the minimization of energies using Merck molecular force field (MMFF) followed by considering distance-dependent dielectric constant of 1.0, convergence criterion or root-mean-square (RMS) gradient at 0.01 kcal/mol Å and the iteration limit to 10,000 (Halgren, 1996). The energy-minimized geometry was used for the calculation of the various 2D descriptors (Individual, Chi, ChiV, Path count, ChiChain, ChiVChain, Chainpathcount, Cluster, Pathcluster, Kapa, Element Count, Estate number, Estate contribution, Semi-impirical, Hydophillic–hydophobic and Polar surface area). The various alignment-independent (AI) descriptors were also calculated. For calculation of alignment, the independent descriptor was assigned the utmost three attributes. The first attribute was T to characterize the topology of the molecule. The second attribute was the atom type, and the third attribute was assigned to atoms taking part in the double or triple bond. The preprocessing of the independent variables (i.e., 2D descriptors) was done by removing invariable (constant column), which resulted in total 153 descriptors to be used for QSAR analysis. In addition to the VLife descriptors, 50 descriptors were also calculated using the Win CAChe version 6.1 modeling software (Fujitsu private limited, Japan).

Table 1 Structures and antimalarial activities of side chain modified 7-chloro-4-aminoquinolines.



4(a-e), 5(a-e) 6(a-b), 7(a-b) 16(a-b) 17(a-b)

Compound	*n*	R	R′	IC_{50} (nM) Dd2	IC_{50} (nM) HB3
4a	2	H	–	129	29.2
4b	3	H	–	56.3	27.3
4c	4	H	–	170	72.5
4d	5	H	–	103	46
4e	6	H	–	269	82.8
5a	2	Et	–	31.2	27.3
5b	3	Et	–	28.1	21.2
5c	4	Et	–	84.6	24.1
5d	5	Et	–	43.4	15.7
5e	6	Et	–	274	62.9
6a	1	Et	–	128	187
6b	1	*i*-Pr	–	99.8	44.1
7a	2	Et	–	882	716
7b	2	*i*-Pr	–	2550	1314
16a	–	Et	Et	80	26.3
16b	–	H	*i*-Pr	51.8	27.8
17a	–	Et	Et	76.1	25.5
17b	–	H	*i*-Pr	75.7	31.3